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CHEMICAL COMPOUNDS

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

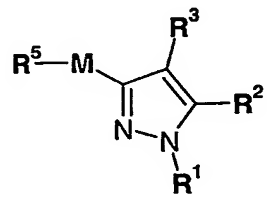
Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The following disclose compounds purported to act as GnRH antagonists: WO 97/21435, WO 97/21703, WO 97/21704, WO 97/21707, WO 55116, WO 98/55119, WO 98/55123, WO 98/55470, WO 98/55479, WO 99/21553, WO 99/21557, WO 99/41251, WO 99/41252, WO 00/04013, WO 00/69433, WO 99/51231, WO 99/51232, WO 99/51233, WO 99/51234, WO 99/51595, WO 99/51596, WO 00/53178, WO 00/53180, WO 00/53179, WO 00/53181, WO 00/53185, WO 00/53602, WO 02/066477, WO 02/066478, WO 02/06645 and WO 02/092565.

It would be desirable to provide further compounds, such compounds being GnRH antagonists. Thus, according to the first aspect of the invention there is provided a compound of Formula (I),



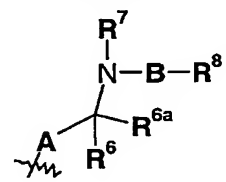
Formula (I)

wherein:

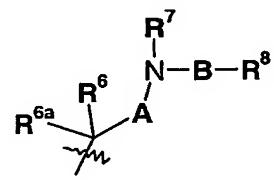
R^1 is selected from: hydrogen, optionally-substituted C_{1-6}alkyl, optionally substituted aryl or optionally-substituted arylC_{1-6}alkyl;

R^2 is an optionally-substituted mono or bi-cyclic aromatic ring;

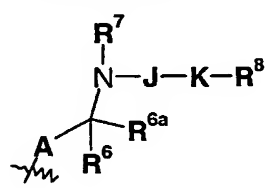
R^3 is selected from a group of Formula (IIa) to Formula (IIf):



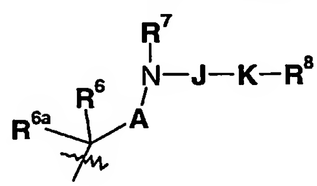
Formula (IIa)



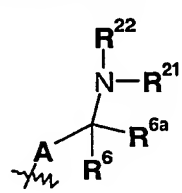
Formula (IIb)



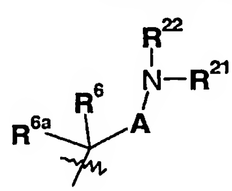
Formula (IIc)



Formula (IId)

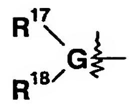


Formula (IIe)



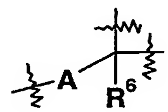
Formula (IIf)

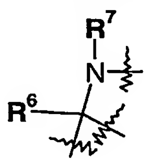
$\mathbf{R^5}$ is a group of Formula (III):



Formula (III)

$\mathbf{R^6}$ and $\mathbf{R^{6a}}$ are independently selected from hydrogen, fluoro, optionally substituted C_{1-6}alkyl, optionally-substituted aryl or optionally substituted arylC_{1-6}alkyl, or $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms, or $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ taken together and the carbon atom to which they are attached form a carbonyl group;

or when **A** is not a direct bond the group  forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

$\mathbf{R^7}$ is selected from: hydrogen, optionally-substituted C_{1-6}alkyl, optionally-substituted arylC_{1-6}alkyl, optionally-substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl, $\mathbf{R^9}$OC_{1-6}alkyl-, $\mathbf{R^9R^{10}}$NC_{1-6}alkyl-, $\mathbf{R^9R^{10}}$NC(O)C_{1-6}alkyl, -C(N$\mathbf{R^9R^{10}}$)=NH;

or when $\mathbf{R^3}$ is a group of Formula (IIc) or (IId) $\mathbf{R^7}$ is of the formula **–J-K-**$\mathbf{R^8}$;

$\mathbf{R^8}$ is selected from:

(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxy, hydroxyC_{1-6}alkyl, cyano, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, C_{1-6}alkyl–S(O_n)-, -O-$\mathbf{R^b}$, –N$\mathbf{R^bR^c}$, –C(O)-$\mathbf{R^b}$, –C(O)O-$\mathbf{R^b}$, -CON$\mathbf{R^bR^c}$, NH-C(O)-$\mathbf{R^b}$ or –S(O_n)N$\mathbf{R^bR^c}$,
where $\mathbf{R^b}$ and $\mathbf{R^c}$ are independently selected from hydrogen and C_{1-4}alkyl optionally substituted with hydroxy, amino, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, HO-C_{2-4}alkyl-NH- or HO-C_{2-4}alkyl-N(C_{1-4}alkyl)-;

(ii) nitro when **B** is a group of Formula (IV) and **X** is CH and **p** is 0;

(iii) C_{3-7}cycloalkyl, aryl or arylC_{1-6}alkyl each of which is optionally substituted by **R**^{12}, **R**^{13} and **R**^{14};

(iv) -(**Q**)-aryl , -(**Q**)-heterocyclyl, -aryl-(**Q**)-aryl, each of which is optionally substituted by **R**^{12}, **R**^{13} and **R**^{14} wherein -(**Q**)- is selected from **E**, **F** or a direct bond;

(v) heterocyclyl or heterocyclylC_{1-6}alkyl each of which is optionally substituted by up to 4 substituents independently selected from **R**^{12}, **R**^{13} and **R**^{14};

(vi) a group selected from **R**^{12}, **R**^{13} and **R**^{14};

R^{9} and **R**^{10} are independently selected from: hydrogen, hydroxy, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl or **R**^{9} and **R**^{10} taken together can form an optionally substituted ring of 3-9 atoms or **R**^{9} and **R**^{10} taken together with the carbon atom to which they are attached form a carbonyl group;

R^{11} is selected from: hydrogen, optionally substituted C_{1-6}alkyl, or N(**R**^{9}**R**^{10});

R^{12} is selected from: hydrogen, hydroxy, **R**^{17}**R**^{18}N(CH_2)$_{cc}$-, **R**^{17}**R**^{18}NC(O)(CH_2)$_{cc}$-, optionally substituted C_{1-6}alkyl- C(O)N(**R**^{9})(CH_2)$_{cc}$-, optionally substituted C_{1-6}alkyl-SO_2N(**R**^{9})-, optionally substituted aryl-SO_2N(**R**^{9})-, C_{1-3}perfluoroalkyl-SO_2N(**R**^{9})-; optionally substituted C_{1-6}alkyl-N(**R**^{9})SO_2-, optionally substituted aryl-N(**R**^{9})SO_2-, C_{1-3}perfluoroalkyl-N(**R**^{9})SO_2- optionally substituted C_{1-6}alkanoyl-N(**R**^{9})SO_2-; optionally substituted aryl-C(O)N(**R**^{9})SO_2-, optionally substituted C_{1-6}alkyl-S(O_n) -, optionally substituted aryl-S(O_n) - , C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted C_{1-6}alkoxy, carboxy, halo, nitro or cyano;

R^{13} and **R**^{14} are independently selected from: hydrogen, hydroxy, oxo, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkanoyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, **R**^{9}O(CH_2)$_s$-, **R**^{9}(O)O(CH_2)$_s$-, **R**^{9}OC(O)(CH_2)$_s$-, **R**^{16}S(O_n)(CH_2)$_s$-, **R**^{9}**R**^{10}NC(O)(CH_2)$_s$- or halo;

R^{15} is selected from: hydrogen, optionally substituted C_{1-6}alkyl, **R**^{19}OC(O)-, **R**^{9}**R**^{10}NC(O)-, **R**^{9}C(O)-, **R**^{9}S(O_n)-;

R^{16} is selected from: hydrogen, C_{1-6}alkyl, C_{1-3}perfluoroalkyl or optionally-substituted aryl;

R^{17} is independently selected from: hydrogen, hydroxy, cyano or optionally substituted C_{1-6}alkyl;

R^{18} is a group of formula **R^{18a}**-C(**R^9R^{10}**)$_{0-1}$- wherein **R^{18a}** is selected from: **R^{19}**OC(O)-, **R^9R^{10}**NC(O)-, **R^9R^{10}**N-, **R^9**C(O)-, **R^9**C(O)N(**R^{10}**)-, **R^9R^{10}**NC(O)-, **R^9R^{10}**NC(O)N(**R^{10}**)-, **R^9**SO_2N(**R^{10}**)-, **R^9R^{10}**NSO_2N(**R^{10}**)-, **R^9**C(O)O-, **R^9**OC(O)-, **R^9R^{10}**NC(O)O-, **R^9**O-, **R^9**S(O_n)-, **R^9R^{10}**NS(O_n) -, hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted heterocyclyl;

or **R^{17}** and **R^{18}** when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;

R^{19} is selected from: hydrogen, optionally substituted C_{1-6}alky, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclylC_{1-6}alkyl;

R^{21} and **R^{22}** are independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl, optionally substituted C_{3-6}alkenyl, optionally substituted C_{3-6}alkynyl, -(C_{1-5}alkyl)$_{aa}$-S(O_n)-(C_{1-5}alkyl)$_{bb}$-; **R^9R^{10}**NC_{2-6}alkyl, **R^9**OC_{2-6}alkyl or **R^9R^{10}**NC(O)C_{2-6}alkyl, with the proviso that **R^9** and **R^{10}** independently or taken together are not optionally substituted aryl or optionally substituted arylC_{1-6}alkyl; or

R^{21} and **R^{22}** taken together form an optionally substituted non-aromatic heterocyclic ring;

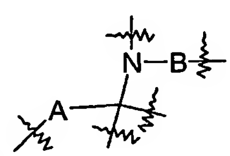
A is selected from:

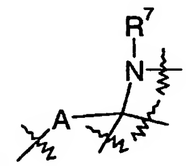
(i) a direct bond;

(ii) optionally-substituted C_{1-5}alkylene wherein the optional substituents are independently selected from: optionally-substituted C_{1-6}alkyl optionally-substituted aryl or optionally substituted arylC_{1-6}alkyl;

(iii) a carbocyclic ring of 3-7 atoms;

(iv) a carbonyl group or –C(O)–C(**R^dR^d**)-, wherein **R^d** is independently selected from hydrogen and C_{1-2}alkyl;

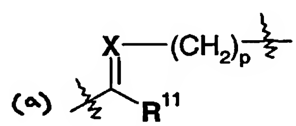
or when **R^3** is a group of Formula (IIa) or (IIb), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

or when $\mathbf{R^3}$ is a group of Formula (IIa), (IIb), (IIc) or (IId), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

B is selected from:

(i) a direct bond;

(ii) a group of Formula (IV)



Formula (IV)

wherein:

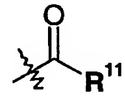
X is selected from N or CH,

wherein at position (a) Formula (IV) is attached to the nitrogen atom and the $(CH_2)_p$ group is attached to $\mathbf{R^8}$; and

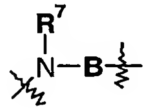
(iii) a group independently selected from: optionally substituted C_{1-6}alkylene, optionally substitute C_{3-7}cycloalkyl, optionally substituted C_{3-6}alkenylene, optionally substituted C_{3-6}alkynyl, C_{1-6}alkoxy, $(C_{1-5}alkyl)_{aa}$-$S(O_n)$-$(C_{1-5}alkyl)_{bb}$-, -$(C_{1-5}alkyl)_{aa}$-O-$(C_{1-5}alkyl)_{bb}$-, -$(C_{1-5}alkyl)_{aa}$-C(O)-$(C_{1-5}alkyl)_{bb}$- or $(C_{1-5}alkyl)_{aa}$-N($\mathbf{R^{15}}$)- $(C_{1-5}alkyl)_{bb}$,

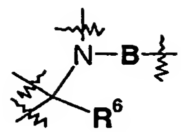
wherein $\mathbf{R^{15}}$ and the $(C_{1-5}alkyl)_{aa}$ or $(C_{1-5}alkyl)_{bb}$ chain can be joined to form a ring, wherein the combined length of $(C_{1-5}alkyl)_{aa}$ and $(C_{1-5}alkyl)_{bb}$ is less than or equal to C_5alkyl;

or the group –**B**-$\mathbf{R^8}$ represents a group of Formula (V)



Formula (V);

or the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms;

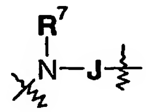
or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

E is –O-, -S(O_n), -C(O)-, -N$\mathbf{R}^{15}$- or -C($\mathbf{R}^9\mathbf{R}^{10}$)$_q$;

F is -**E**(CH_2)$_r$-;

G is selected from: hydrogen, halo, N, O, S(O_n), C(O), C($\mathbf{R}^9\mathbf{R}^{10}$)$_t$, optionally substituted C_{2-6}alkenylene, optionally substituted C_{2-6}alkynylene or a direct bond to $\mathbf{R}^{18}$,

J is a group of the formula: -(CH_2)$_s$-**L**-(CH_2)$_s$- wherein when **s** is greater than 0, the alkylene group is optionally substituted,

or the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms;

K is selected from: a direct bond, -(CH_2)$_{s1}$-, -(CH_2)$_{s1}$-O-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-C(O)-(CH_2)$_{s2}$- , -(CH_2)$_{s1}$-S(O_n)-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-N($\mathbf{R}^{18}$)-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-C(O)N($\mathbf{R}^9$)-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-N($\mathbf{R}^9$)C(O)-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-N($\mathbf{R}^9$)C(O)N($\mathbf{R}^9$)-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-OC(O)-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-C(O)O-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-N($\mathbf{R}^9$)C(O)O-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-OC(O)N($\mathbf{R}^9$)-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-OS(O_n)-(CH_2)$_{s2}$-, or -(CH_2)$_{s1}$-S(O_n)-O-(CH_2)$_{s2}$-, -(CH_2)$_{s1}$-S(O)$_2$N($\mathbf{R}^9$)-(CH_2)$_{s2}$-or -(CH_2)$_{s1}$-N($\mathbf{R}^9$)S(O)$_2$-(CH_2)$_{s2}$-; wherein the -(CH_2)$_{s1}$- and -(CH_2)$_{s2}$- groups are independently optionally substituted by hydroxy or C_{1-4}alkyl;

L is selected from optionally substituted aryl or optionally substituted heterocyclyl;

M is selected from –(CH_2)$_{0-2}$-O- or –C(O)NH-;

n is an integer from 0 to 2;

p is an integer from 0 to 4;

q is an integer from 0 to 4;

r is an integer from 0 to 4;

s is an integer from 0 to 4;

s1 and **s2** are independently selected from an integer from 0 to 4, and **s1+s2** is less than or equal to 4;

t is an integer between 0 and 4; and

aa and **bb** are independently 0 or 1;

cc is an integer between 0 to 2;

with the proviso that

(i) when **G** is hydrogen or halo, then $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are both absent;

(ii) when **G** is O, S(O_n), C(O) or C($\mathbf{R^{11}R^{12}}$)$_t$ then **G** is substituted by a single group independently selected from the definition of $\mathbf{R^{17}}$ or $\mathbf{R^{18}}$ and when **G** is a direct bond to $\mathbf{R^{18}}$ then **G** is substituted by a single group selected from $\mathbf{R^{18}}$;

(iii) when $\mathbf{R^3}$ is a group of Formula (IIb), **B** is a group of Formula (IV), $\mathbf{R^8}$ is selected from group (i) or (ii) above, $\mathbf{R^{11}}$ is a group of the formula N($\mathbf{R^{10}R^{11}}$) and $\mathbf{R^1}$, $\mathbf{R^2}$ and $\mathbf{R^5}$ are as defined above then $\mathbf{R^4}$ cannot be hydrogen;

(iv) $\mathbf{R^3}$ cannot be unsubstituted pyridyl or unsubstituted pyrimidinyl; and

(v) when $\mathbf{R^3}$ is pyrazolyl substituted by phenyl or pyrazolyl substituted by phenyl and acetyl, $\mathbf{R^5}$-**M** is hydroxyl or acetyloxy, $\mathbf{R^2}$ is unsubstituted phenyl, then $\mathbf{R^1}$ cannot be hydrogen or acetyl;

or a salt, solvate or pro-drug thereof.

According to the further feature of the first aspect of the invention there is provided a compound of Formula (I)with the proviso that

(i) when **G** is hydrogen or halo, then $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are both absent;

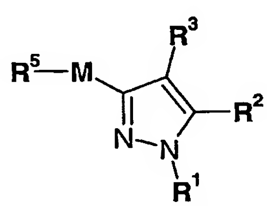
(ii) when **G** is O, S(O_n), C(O) or C($\mathbf{R^{11}R^{12}}$)$_t$ then **G** is substituted by a single group independently selected from the definition of $\mathbf{R^{17}}$ or $\mathbf{R^{18}}$ and when **G** is a direct bond to $\mathbf{R^{18}}$ then **G** is substituted by a single group selected from $\mathbf{R^{18}}$;

(iii) when $\mathbf{R^3}$ is a group of Formula (IIb), **B** is a group of Formula (IV), $\mathbf{R^8}$ is selected from group (i) or (ii) above, $\mathbf{R^{11}}$ is a group of the formula N($\mathbf{R^{10}R^{11}}$) and $\mathbf{R^1}$, $\mathbf{R^2}$ and $\mathbf{R^5}$ are as defined above then $\mathbf{R^4}$ cannot be hydrogen; and

(iv) $\mathbf{R^3}$ cannot be an unsubstituted or substituted aromatic heterocyclic ring, wherein the aromatic heterocyclic ring is attached directed to the pyrazole in Formula (I);

or a salt, solvate or pro-drug thereof.

According to the further feature of the first aspect of the invention there is provided a compound of Formula (Ia),



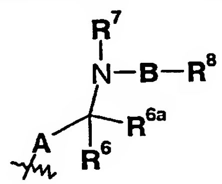
Formula (Ia)

wherein:

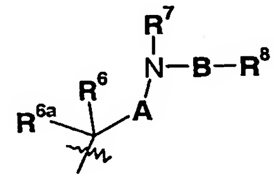
R^1 is selected from: hydrogen, optionally-substituted C_{1-6}alkyl, optionally substituted aryl or optionally-substituted arylC_{1-6}alkyl;

R^2 is an optionally-substituted mono or bi-cyclic aromatic ring;

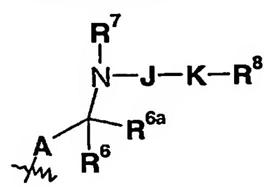
R^3 is selected from a group of Formula (IIa) to Formula (IIf):



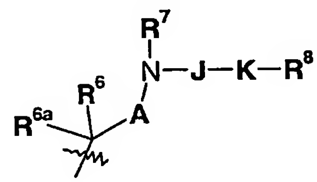
Formula (IIa)



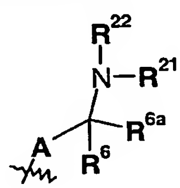
Formula (IIb)



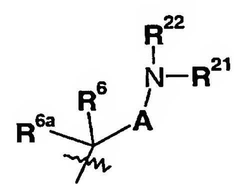
Formula (IIc)



Formula (IId)

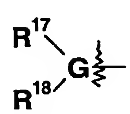


Formula (IIe)



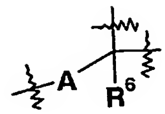
Formula (IIf)

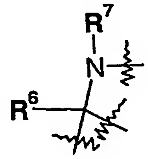
R^5 is a group of Formula (III):



Formula (III)

R^6 and R^{6a} are independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally-substituted aryl or optionally substituted arylC_{1-6}alkyl, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbonyl group;

or when **A** is not a direct bond the group  forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

$\mathbf{R^7}$ is selected from: hydrogen, optionally-substituted C_{1-6}alkyl, optionally-substituted arylC_{1-6}alkyl, optionally-substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl, $\mathbf{R^9}$OC_{1-6}alkyl-, $\mathbf{R^9R^{10}}$NC_{1-6}alkyl-, $\mathbf{R^9R^{10}}$NC(O)C_{1-6}alkyl, -C(NR^{9}R^{10})=NH;

or when $\mathbf{R^3}$ is a group of Formula (IIc) or (IId) $\mathbf{R^7}$ is of the formula **–J-K-R^8**;

$\mathbf{R^8}$ is selected from:

(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxy, hydroxyC_{1-6}alkyl, cyano, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, C_{1-6}alkyl–S(O_n)-, -O-$\mathbf{R^b}$, –N$\mathbf{R^bR^c}$, –C(O)-$\mathbf{R^b}$, –C(O)O-$\mathbf{R^b}$, -CON$\mathbf{R^bR^c}$ or NH-C(O)-$\mathbf{R^b}$,

where $\mathbf{R^b}$ and $\mathbf{R^c}$ are independently selected from hydrogen and C_{1-4}alkyl optionally substituted with hydroxy, amino, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, HO-C_{2-4}alkyl-NH- or HO-C_{2-4}alkyl-N(C_{1-4}alkyl)-;

(ii) nitro when **B** is a group of Formula (IV) and **X** is CH and **p** is 0;

(iii) C_{3-7}cycloalkyl, aryl or arylC_{1-6}alkyl each of which is optionally substituted by $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;

(iv) -(**Q**)-aryl , -(**Q**)-heterocyclyl, -aryl-(**Q**)-aryl, each of which is optionally substituted by $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$

wherein -(**Q**)- is selected from **E**, **F** or a direct bond;

(v) heterocyclyl or heterocyclylC_{1-6}alkyl each of which is optionally substituted by $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;

(vi) a group selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently selected from: hydrogen, hydroxy, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, an optionally

substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl or $\mathbf{R^9}$ and $\mathbf{R^{10}}$ taken together can form an optionally substituted ring of 3-9 atoms or $\mathbf{R^9}$ and $\mathbf{R^{10}}$ taken together with the carbon atom to which they are attached form a carbonyl group;

$\mathbf{R^{11}}$ is selected from: hydrogen, optionally substituted C_{1-6}alkyl, or $N(\mathbf{R^9R^{10}})$;

$\mathbf{R^{12}}$ is selected from: hydrogen, hydroxy, $\mathbf{R^{17}R^{18}}N$-, optionally substituted C_{1-6}alkyl-$SO_2N(\mathbf{R^9})$-, optionally substituted aryl-$SO_2N(\mathbf{R^9})$-, C_{1-3}perfluoroalkyl-$SO_2N(\mathbf{R^9})$-; optionally substituted C_{1-6}alkyl-$N(\mathbf{R^9})SO_2$-, optionally substituted aryl-$N(\mathbf{R^9})SO_2$-, C_{1-3}perfluoroalkyl-$N(\mathbf{R^9})SO_2$- optionally substituted C_{1-6}alkanoyl-$N(\mathbf{R^9})SO_2$-; optionally substituted aryl-$C(O)N(\mathbf{R^9})SO_2$-, optionally substituted C_{1-6}alkyl-$S(O_n)$ -, optionally substituted aryl-$S(O_n)$ - , C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted C_{1-6}alkoxy, carboxy, halo, nitro or cyano;

$\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ are independently selected from: hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $\mathbf{R^9}O(CH_2)_s$-, $\mathbf{R^9}(O)O(CH_2)_s$-, $\mathbf{R^9}OC(O)(CH_2)_s$-, $\mathbf{R^{16}}S(O_n)(CH_2)_s$-, $\mathbf{R^9R^{10}}NC(O)(CH_2)_s$- or halo;

$\mathbf{R^{15}}$ is selected from: hydrogen, optionally substituted C_{1-6}alkyl, $\mathbf{R^{19}}OC(O)$-, $\mathbf{R^9R^{10}}NC(O)$-, $\mathbf{R^9}C(O)$-, $\mathbf{R^9}S(O_n)$-;

$\mathbf{R^{16}}$ is selected from: hydrogen, C_{1-6}alkyl, C_{1-3}perfluoroalkyl or optionally-substituted aryl;

$\mathbf{R^{17}}$ is independently selected from: hydrogen, hydroxy, cyano or optionally substituted C_{1-6}alkyl;

$\mathbf{R^{18}}$ is a group of formula $\mathbf{R^{18a}}$-$C(\mathbf{R^9R^{10}})_{0-1}$- wherein $\mathbf{R^{18a}}$ is selected from: $\mathbf{R^{19}}OC(O)$-, $\mathbf{R^9R^{10}}NC(O)$-, $\mathbf{R^9R^{10}}N$-, $\mathbf{R^9}C(O)$-, $\mathbf{R^9}C(O)N(\mathbf{R^{10}})$-, $\mathbf{R^9R^{10}}NC(O)$-, $\mathbf{R^9R^{10}}NC(O)N(\mathbf{R^{10}})$-, $\mathbf{R^9}SO_2N(\mathbf{R^{10}})$-, $\mathbf{R^9R^{10}}NSO_2N(\mathbf{R^{10}})$-, $\mathbf{R^9}C(O)O$-, $\mathbf{R^9}OC(O)$-, $\mathbf{R^9R^{10}}NC(O)O$-, $\mathbf{R^9}O$-, $\mathbf{R^9}S(O_n)$-, $\mathbf{R^9R^{10}}NS(O_n)$ -, optionally substituted C_{1-6}alkyl, optionally substituted heterocyclyl;

or $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;

$\mathbf{R^{19}}$ is selected from: hydrogen, optionally substituted C_{1-6}alky, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclylC_{1-6}alkyl;

$\mathbf{R^{20}}$ is selected from $\mathbf{R^{12}}$ or $\mathbf{R^{13}}$;

R^{21} and **R^{22}** are independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl, optionally substituted C_{3-6}alkenyl, optionally substituted C_{3-6}alkynyl, -(C_{1-5}alkyl)$_{aa}$-S(O_n)-(C_{1-5}alkyl)$_{bb}$-; **R^{9}R^{10}**NC_{2-6}alkyl, **R^9**OC_{2-6}alkyl or **R^{9}R^{10}**NC(O)C_{2-6}alkyl, with the proviso that **R^9** and **R^{10}** independently or taken together are not optionally substituted aryl or optionally substituted arylC_{1-6}alkyl; or

R^{21} and **R^{22}** taken together form an optionally substituted non-aromatic heterocyclic ring;

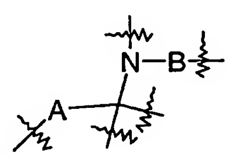
A is selected from:

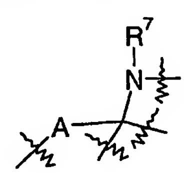
(i) a direct bond;

(ii) optionally-substituted C_{1-5}alkylene wherein the optional substituents are independently selected from: optionally-substituted C_{1-6}alkyl optionally-substituted aryl, optionally substituted arylC_{1-6}alkyl or substituted arylC_{1-6}alkyl;

(iii) a carbocyclic ring of 3-7 atoms;

(iv) a carbonyl group;

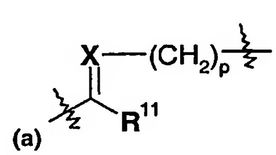
or when **R^3** is a group of Formula (IIa) or (IIb), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

or when **R^3** is a group of Formula (IIa), (IIb), (IIc) or (IId), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

B is selected from:

(i) a direct bond;

(ii) a group of Formula (IV)



Formula (IV)

wherein:

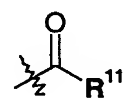
X is selected from N or CH,

wherein at position (a) Formula (IV) is attached to the nitrogen atom and the $(CH_2)p$ group is attached to $\mathbf{R^8}$; and

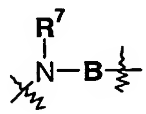
(iii) a group independently selected from: optionally substituted $C_{1\text{-}6}$alkylene, optionally substitute $C_{3\text{-}7}$cycloalkyl, optionally substituted $C_{3\text{-}6}$alkenylene, optionally substituted $C_{3\text{-}6}$alkynyl, $C_{1\text{-}6}$alkoxy, $(C_{1\text{-}5}alkyl)_{aa}$-$S(O_n)$-$(C_{1\text{-}5}alkyl)_{bb}$-, $(C_{1\text{-}5}alkyl)_{aa}$-O-$(C_{1\text{-}5}alkyl)_{bb}$- or $(C_{1\text{-}5}alkyl)_{aa}$-$N(\mathbf{R^{15}})$- $(C_{1\text{-}5}alkyl)_{bb}$,

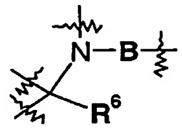
wherein $\mathbf{R^{15}}$ and the $(C_{1\text{-}5}alkyl)_{aa}$ or $(C_{1\text{-}5}alkyl)_{bb}$ chain can be joined to form a ring;

or the group **–B-R⁸** represents a group of Formula (V)



Formula (V);

or the group  together forms a heterocyclic ring containing 5-7 carbons atoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

E is –O-, -$S(O_n)$, -C(O)-, -$\mathbf{NR^{15}}$- or -$C(\mathbf{R^9R^{10}})_q$;

F is -$\mathbf{E}(CH_2)_r$-;

G is selected from: hydrogen, halo, N, O, $S(O_n)$, C(O), $C(\mathbf{R^9R^{10}})_t$, optionally substituted $C_{2\text{-}6}$alkenylene, optionally substituted $C_{2\text{-}6}$alkynylene or a direct bond to $\mathbf{R^{18}}$,

J is a group of the formula: -$(CH_2)_s$-**L**-$(CH_2)_s$- wherein when s is greater than 0, the alkylene group is optionally substituted

K is selected from: a direct bond, -O-$(CH_2)_s$-, -C(O)-$(CH_2)_s$- , -$S(O_n)$ -$(CH_2)_s$-, -$N(\mathbf{R^{18}})$-$(CH_2)_s$-, -OC(O)-$(CH_2)_s$-, -C(O)O-$(CH_2)_s$-, -$OS(O_n)$-$(CH_2)_s$-, or -$S(O_n)$-O-$(CH_2)_s$-;

L is selected from optionally substituted aryl or optionally substituted heterocyclyl;

M is –$(CH_2)_{0\text{-}2}$-O-;

n is an integer between 0 and 2;

p is an integer between 0 and 4;

q is an integer between 0 and 4;

r is an integer between 0 and 4;

s is an integer between 0 and 4; and

t is an integer between 0 and 4;

with the proviso that

(i) when **G** is hydrogen or halo, then $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are both absent;

(ii) when **G** is O, $S(O_n)$, C(O) or $C(\mathbf{R^{11}R^{12}})_t$ then **G** is substituted by a single group independently selected from the definition of $\mathbf{R^{17}}$ or $\mathbf{R^{18}}$ and when G is a direct bond to $\mathbf{R^{18}}$ then **G** is substituted by a single group selected from $\mathbf{R^{18}}$; and

or a salt, solvate or pro-drug thereof.

According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (I) or Formula (Ia), or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the first aspect of the invention there is provided the following uses of a compound of Formula (I) or Formula (Ia), or salt, pro-drug or solvate thereof:

(a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;

(b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and

(c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient, preferably a sex hormone related condition selected from prostate cancer and pre-menopausal breast cancer.

According to a further aspect of the invention there is provided a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering a compound of Formula (I) or Formula (Ia), or salt, pro-drug or solvate thereof, to a patient.

Whilst pharmaceutically-acceptable salts of compounds of the invention are preferred, other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

Whilst the invention comprises compounds of the invention, and salts, pro-drugs or solvates thereof, in a further embodiment of the invention, the invention comprises compounds of the invention and salts thereof.

In the present specification, unless otherwise indicated, an **alkyl, alkylene, alkenyl** or **alkynyl** moiety may be linear or branched. The term "**alkylene**" refers to the group $-CH_2-$. Thus, C_8 alkylene for example is $-(CH_2)_8-$. For avoidance of doubt the term C_0alkyl within the group C_{0-5}alkyl is a direct bond.

The term '**propylene**' refers to trimethylene and the branched alkyl chains $-CH(CH_3)CH_2-$ and $-CH_2-CH(CH_3)-$. The straight chain propylene di-radical is preferred, i.e. $-CH_2CH_2CH_2-$. Specific propylene radicals refer to the particular structure, thus the term, propyl-2-ene refers to the group $-CH_2-CH(CH_3)-$. Similar notation is used for other divalent alkyl chains such as butylene.

The term '**2-propenyl**' refers to the group $-CH_2-CH=CH-$.

The term "**aryl**" refers to phenyl or naphthyl.

The term "**carbamoyl**" refers to the group $-C(O)NH_2$.

The term "**halo**" refers to fluoro, chloro, bromo or iodo.

The term "**heterocyclyl**" or "**heterocyclic ring**" refers to a 4-12 membered, preferably 5-10 membered aromatic mono or bicyclic ring or a 4-12 membered, preferably 5-10 membered saturated or partially saturated mono or bicyclic ring, said aromatic, saturated or partially unsaturated rings containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered aromatic heterocyclic rings include pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. A 9 or 10 membered bicyclic aromatic heterocyclic ring is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuranyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, indolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, cinnolinyl and naphthyridinyl. Examples of saturated or partially saturated heterocyclic rings include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl, benzodioxyl and dihydropyrimidinyl.

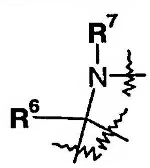
This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or S(O2) group.

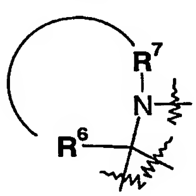
The term "**aromatic ring**" refers to a 5-10 membered aromatic mono or bicyclic ring optionally containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur. Examples of such "aromatic rings" include: phenyl, pyrrolyl, pyrazolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. Preferred aromatic rings include phenyl, thienyl and pyridyl.

The symbol  denotes where the respective group is linked to the remainder of the molecule.

For the avoidance of doubt where two groups or integers appear within the same definition, for example, $-(CH_2)_s$-L-$(CH_2)_s$- or $\mathbf{R^9R^{10}}NSO_2N(\mathbf{R^{10}})$-, then these can be the same of different.

For the avoidance of doubt, where several groups together form a ring, for example:

'the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms', then the groups shown cyclises to form a ring, i.e

 the component of which are defined by the definitions of the groups which form the ring, thus in the above example the ring would include a nitrogen atom. For example in Example 5 this group forms a piperazine ring.

The term $\mathbf{C_{1\text{-}3}}$**perfluoroalkyl** refers to a $C_{1\text{-}3}$alkyl chain in which all hydrogens have been replaced with a fluorine atom. Examples of $\mathbf{C_{1\text{-}3}}$**perfluoroalkyl** include trifluoromethyl, pentafluoroethyl and 1-trifluoromethyl-1,2,2,2-tetrafluoroethyl-. Preferably $\mathbf{C_{1\text{-}3}}$**perfluoroalkyl** is trifluromethyl.

Examples of $\mathbf{C_{1\text{-}8}}$**alkyl** include: methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *tert*-butyl and 2-methyl-pentyl; example of $\mathbf{C_{1\text{-}8}}$**alkylene** include: methylene, ethylene and 2-methyl-propylene; examples of $\mathbf{C_{1\text{-}6}}$**alkenyl** include allyl (2-propenyl) and 2—butenyl,

examples of **C_{1-6}alkynyl** 2-propynyl and 3-butynyl, examples of **haloC_{1-6}alkyl** include fluoroethyl, chloropropyl and bromobutyl, examples of **hydroxyC_{1-6}alkyl** include hydroxymethyl, hydroxyethyl and hydroxybutyl, examples of **C_{1-8}alkoxy** include methoxy, ethoxy and butyloxy; examples of **C_{1-4}alkoxyC_{1-4}alkyl** include methoxyethyl, propoxybutyl and propoxymethyl, examples of **C_{1-6}alkanoyl** incude formyl, ethanoyl, propanoyl or pentanoyl, examples of **N-C_{1-4}alkylamino** include N-methylamino and N-ethylamino; examples of **N,N-di-C_{1-4}alkylamino** include N,N-dimethylaminoethyl, N,N-di-methylaminopropyl and N,N-dipropylaminoethyl, examples of **HO-C_{2-4}alkyl-NH** include hydroxymethylamino hydroxyethylamino and hydroxypropyamino, examples of **HO-C_{2-4}alkyl-N(C_{1-4}alkyl)** include N-methyl-hydroxymethylamino, N-ethyl-hydroxyethylamino, and N-propyl-hydroxypropyamino, examples of C_{1-6}alkyl-S(O_n)-methylthio, methylsulphinyl, ethylsulphinyl, ethylsulphonyl and propylsulphonyl, include examples of **arylC_{1-6}alkyl** include benzyl, phenethyl and phenylbutyl, examples of **heterocyclylC_{1-6}alkyl** include pyrrolidin-1-yl ethyl, imidazolylethyl, pyridylmethyl and pyrimidinylethyl.

It is to be understood that, insofar as certain of the compounds of the invention may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of antagonizing gonadotropin releasing hormone (GnRH) activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the different features of the invention that possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

Preferred compounds of Formula (I), Formula (Ia) and Formula (Ib) are those wherein any one of the following apply.

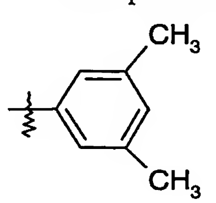
Preferably $\mathbf{R^1}$ is selected from hydrogen or optionally substituted C_{1-6}alkyl. More preferably $\mathbf{R^1}$ represents hydrogen or unsubstituted C_{1-6}alkyl. Yet more preferably $\mathbf{R^1}$ represents hydrogen, methyl, ethyl or *tert*-butyl. Most preferably $\mathbf{R^1}$ represents hydrogen.

Preferably optional substituents on $\mathbf{R^1}$ are independently selected from: optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $\mathbf{R^9}O(CH_2)_v$-; $\mathbf{R^9}C(O)O(CH_2)_v$-, $\mathbf{R^9}OC(O)(CH_2)_v$-, $\mathbf{R^{16}}S(O_n)(CH_2)_v$-, $\mathbf{R^9R^{10}}NC(O)(CH_2)_v$-, or halo wherein **v** is an integer between 0 and 4, and where 2 optional substituents are present together they can optionally form a C_{3-7}carbocyclic ring or a heterocyclic ring.

Preferably $\mathbf{R^2}$ is an optionally substituted monocyclic aromatic ring structure. Most preferably $\mathbf{R^2}$ represents optionally substituted phenyl.

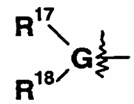
Preferably optional substituents on $\mathbf{R^2}$ are independently selected from: optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $\mathbf{R^9}O(CH_2)_p$-, $\mathbf{R^9}C(O)O(CH_2)_w$-, $\mathbf{R^9}OC(O)(CH_2)_w$-, $\mathbf{R^{16}}S(O_n)(CH_2)_w$-, $\mathbf{R^9R^{10}}NC(O)(CH_2)_w$-, $\mathbf{R^9R^{10}}N$- or halo; wherein **w** is an integer between 0 and 4 and $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are as defined above. Further preferably the optional substituents on $\mathbf{R^2}$ are independently selected from cyano, $\mathbf{R^eR^f}N$-, optionally substituted C_{1-6}alkyl (preferably, C_{1-4}alkyl, eg, methyl or ethyl), optionally substituted C_{1-6}alkoxy (preferably, C_{1-4}alkoxy, eg, methoxy, ethoxy or *tert*-butoxy) or halo (eg, F, Br or Cl) wherein $\mathbf{R^e}$ and $\mathbf{R^f}$ are independently selected from hydrogen, C_{1-6}alkyl or aryl. Yet further preferably optional substituents on $\mathbf{R^2}$ are independently selected from methyl, ethyl, methoxy, ethoxy, *tert*-butoxy, F or Cl. Most preferably optional substituents on $\mathbf{R^2}$ are independently selected from methyl, F or Cl. Preferably $\mathbf{R^2}$ bears 1, 2 or 3 substituents.

Most preferably $\mathbf{R^2}$ represents



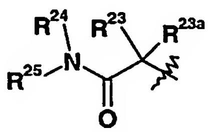
Preferably $\mathbf{R^3}$ is selected from a group of Formula (IIa) Formula (IIb), Formula (IIc) or Formula (IId). Further preferably R^3 is selected from Formula (IIa) or Formula (IIb). Most preferably $\mathbf{R^3}$ is a group of Formula (IIb).

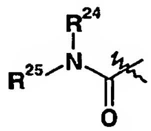
Preferably the group of Formula (III):

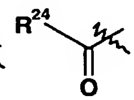


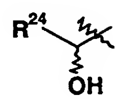
Formula (III)

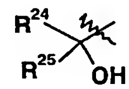
is selected from a group of Formula **III-a**; **III-b**; **III-c**; **III-d**; **III-e**; **III-f**, **III-g** , **III-h**, **III-i**, or **III-j**, **III-k** or **III-l**;

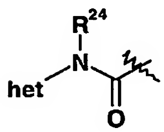

III-a

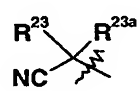

III-b

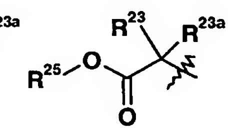

III-c

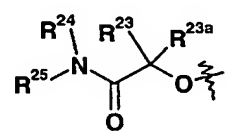

III-d

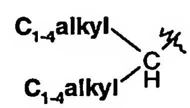

III-e

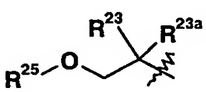

III-f

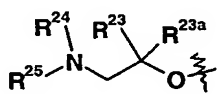

III-g


III-h


III-i


III-j


III-k


III-l

wherein:

het represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

$\mathbf{R^{23}}$ and $\mathbf{R^{23a}}$ are independently selected from:

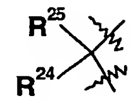
(i) hydrogen or optionally substituted C_{1-8}alkyl; or

(ii) $\mathbf{R^{23}}$ and $\mathbf{R^{23a}}$ together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

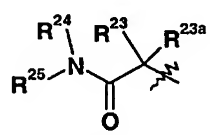
$\mathbf{R^{24}}$ and $\mathbf{R^{25}}$ are selected from:

(i) $\mathbf{R^{24}}$ selected from hydrogen; optionally substituted C_{1-8}alkyl; optionally substituted aryl; -$\mathbf{R^{d}}$-Ar, where $\mathbf{R^{d}}$ represents C_{1-8}alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and $\mathbf{R^{25}}$ is selected from hydrogen; optionally substituted C_{1-8}alkyl and optionally substituted aryl;

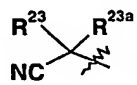
(ii) wherein the group of Formula (III) represents a group of Formula **III-a** , **III-b** or **III-i**, then the group $NR^{24}(-R^{25})$ represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

(iii) wherein the group of Formula (III) represents structure **III-e**,  represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

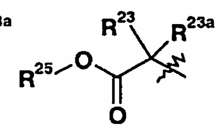
More preferably the group of Formula (III) is selected from a group of Formula **III-a** , **III-g**, **III-h**, **III-i**, **III-j**, **III-k** or **III-l**:



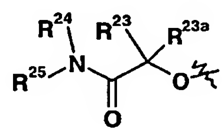
III-a



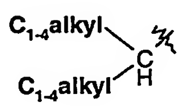
III-g



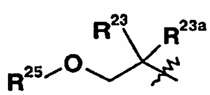
III-h



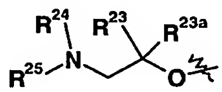
III-i



III-j



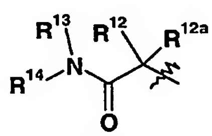
III-k



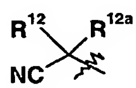
III-l

wherein R^{23}, R^{23a}, R^{24} and R^{25} are as defined above.

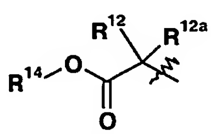
Further preferably the group of Formula (III) is selected from one of the following groups:



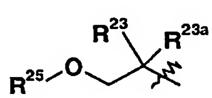
III-a



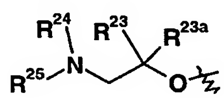
III-g



III-h



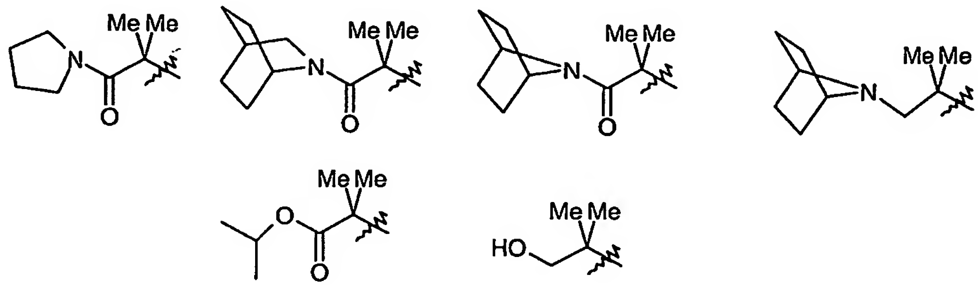
III-k



III-l

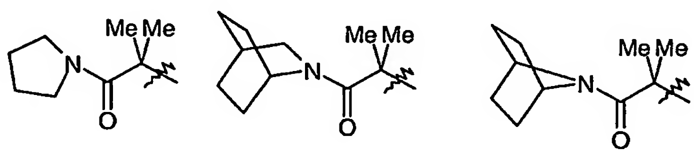
wherein R^{23}, R^{23a}, R^{24} and R^{25} are as defined above.

Yet further preferably the group of Formula (III) is selected from one of the following groups:

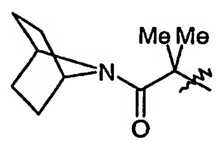


wherein Me represents methyl.

Yet further preferably the group of Formula (III) is selected from one of the following groups:



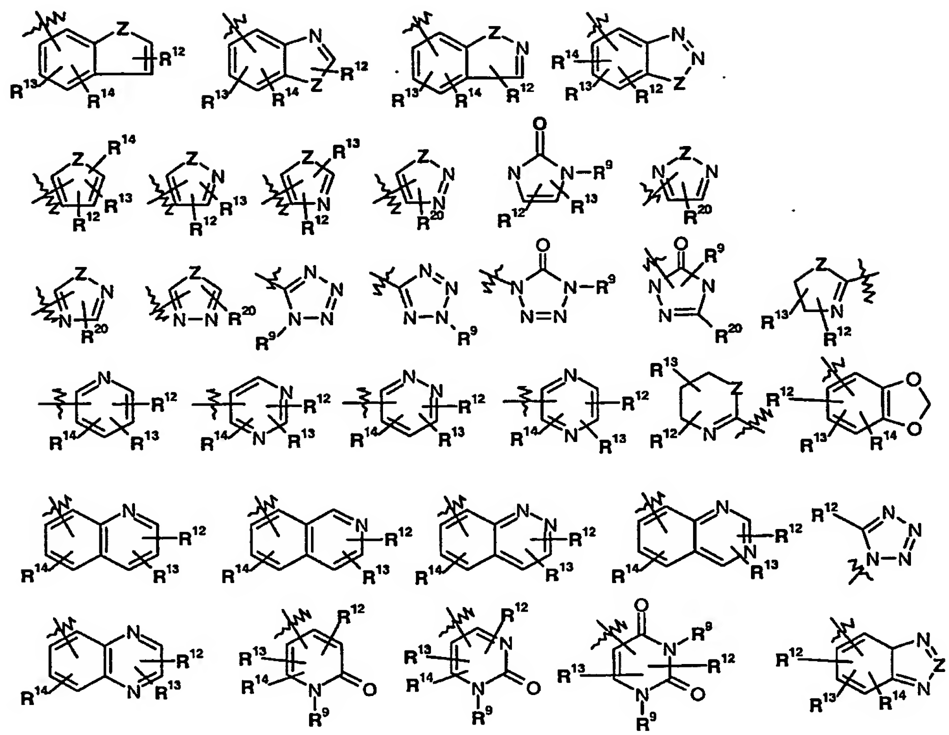
Most preferably the group of Formula (III) is:



Preferably R^6 and R^{6a} are independently selected from hydrogen, fluoro, optionally substituted C_{1-6}alkyl or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms More preferably R^6 and R^{6a} are independently selected from hydrogen, unsubstituted C_{1-6}alkyl or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms. Yet more preferably R^6 and R^{6a} are independently selected from hydrogen, methyl or R^6 and R^{6a} taken together and the carbon atom to which they are attached form cyclopropyl. Most preferably R^6 is hydrogen and R^{6a} is methyl.

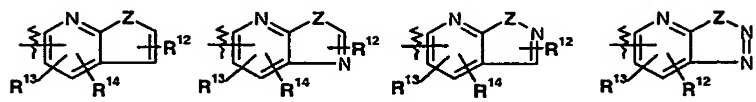
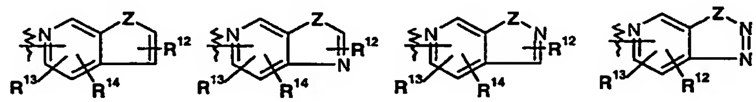
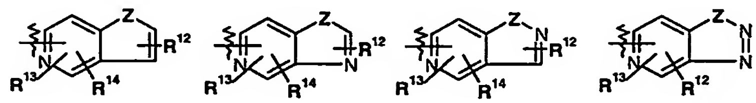
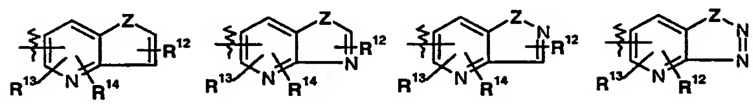
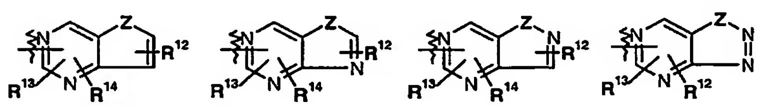
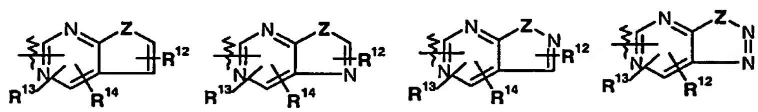
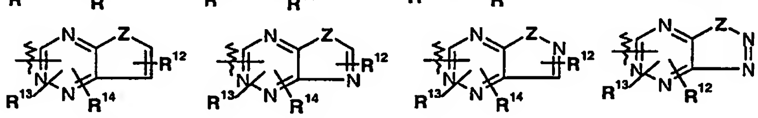
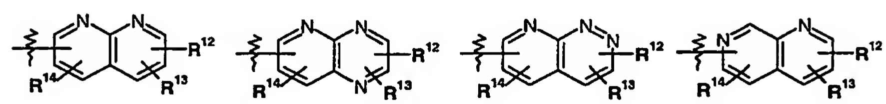
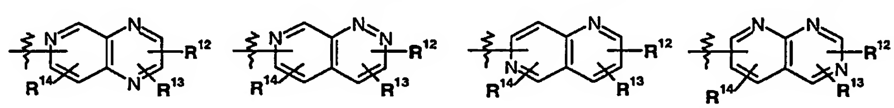
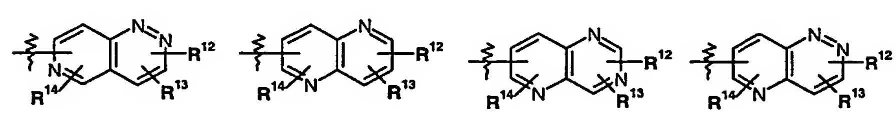
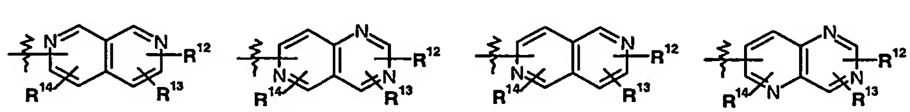
Preferably R^7 is selected from: hydrogen or C_{1-4}alkyl. More preferably R^7 is hydrogen or methyl. Most preferably R^7 is hydrogen.

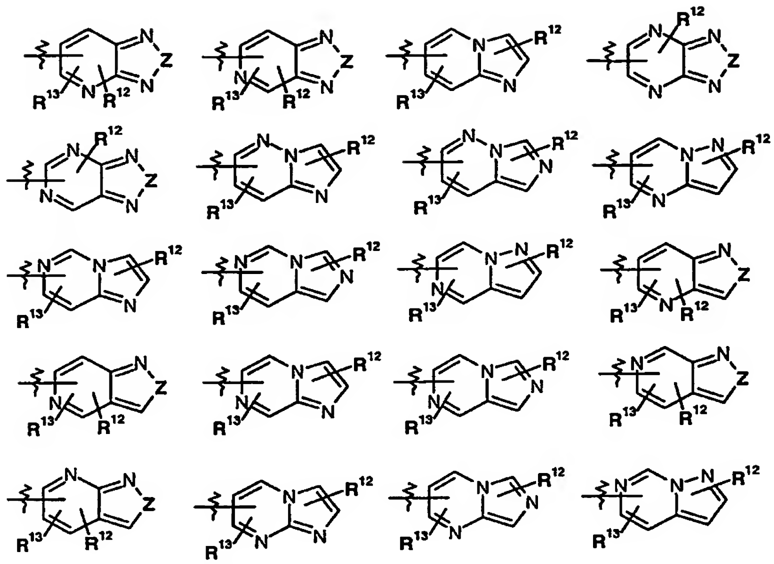
When R^8 is heterocyclyl then R^8 is preferably selected from one of the following groups:



wherein **Z** is selected from: O, S or N(**R**^{9}), **R**^{20} is selected form any group within the definitions of **R**^{12} and **R**^{13}, and **R**^{9}, **R**^{12}, **R**^{13} and **R**^{14} are as defined above.

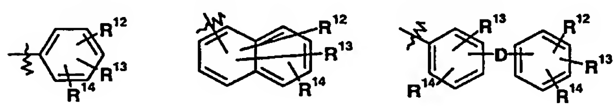
In a further embodiment of the invention when **R**^{8} is heterocyclyl then **R**^{8} is preferably selected from one of the following groups:



wherein **Z** is selected from: O, S or N($\mathbf{R^9}$) and $\mathbf{R^9}$, $\mathbf{R^{12}}$ and $\mathbf{R^{13}}$ are as defined above.

When $\mathbf{R^8}$ is aryl or aryl-(C)-aryl optionally substituted by $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$, $\mathbf{R^8}$ is preferably selected one of the following groups:



wherein **D** is selected from group **E**, group **F** or a direct bond;

Preferably $\mathbf{R^8}$ is selected from

(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, haloC_{1-6}alkyl, hydroxy, cyano, C_{1-6}alkylS(O_n)-, -O-$\mathbf{R^b}$, C_{1-4}alkoxyC_{1-4}alkyl, -C(O)-$\mathbf{R^b}$, C(O)O-$\mathbf{R^b}$, -NH-C(O)-$\mathbf{R^b}$, N,N-di-C_{1-4}alkylamino, -S(O_n)N$\mathbf{R^b}\mathbf{R^c}$
where $\mathbf{R^b}$ and $\mathbf{R^c}$ are independently selected from hydrogen and C_{1-6}alkyl, and **n** is 0, 1 or 2;

(ii) -(**Q**)-aryl, optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;

(iii) C_{4-7}heterocyclyl, optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$,
more preferably selected from: azirinyl, azetidinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, hexahydrotriazinyl, tetraydrotriazinyl, dihydrotriazinyl, tetrahydrofuranyl, dioxolanyl, tetrahydropyranyl, dioxanyl, trioxanyl, tetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothienyl

tetrahydrothiopyran, 1-oxotetrahydrothiopyran, 1,1-dioxotetrahydrothiopyran, dithianyl, trithianyl, morpholinyl, oxathiolanyl, oxathianyl, thiomorpholinyl, thiazinanyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, thiazolidinyl, pyrrolyl, imidazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, thiazolyl, thiadiazolyl, thiadiazinyl, oxazolyl, isoxazolyl, oxadiazolyl, furazanyl, octahydropyrrolopyrrolyl, octahydropyrrolopyrrolyl,benzotriazolyl, dihydrobenzotriazolyl, indolyl, indolinyl, benzimidazolyl, 2,3-dihydrobenzimidazoly, benzotriazolyl 2,3-dihydro benzotriazolyl quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinozalinyl, naphthyridinyl, pteridinyl, benzodioxolyl, tetrahydrodioxolopyrrolyl, 1,5-dioxa-9-azaspiro[5.5]undecanyl or 8-oxa-3-azabicyclooctanyl; each of which is optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ or

(iv) $C_{3\text{-}7}$carbocyclyl; optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;

Further preferably $\mathbf{R^{8}}$ is selected from

(i) hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, halo$C_{1\text{-}6}$alkyl, hydroxy, cyano, $C_{1\text{-}6}$alkylS(O_n)-, -O-$\mathbf{R^b}$, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkyl, -C(O)-$\mathbf{R^b}$, C(O)O-$\mathbf{R^b}$, -NH-C(O)-$\mathbf{R^b}$, N,N-di-$C_{1\text{-}4}$alkylamino, -S(O_n)N$\mathbf{R^b}\mathbf{R^c}$

where $\mathbf{R^b}$ and $\mathbf{R^c}$ are independently selected from hydrogen and $C_{1\text{-}6}$alkyl, and **n** is 0, 1 or 2;

preferably selected from: hydrogen, methyl, isopropyl, *t*-butyl, 1-methylethyl, allyl, fluoroethyl, hydroxy, cyano, ethylsulphonyl, methoxy, 1-methyl-2-methoxyethyl, acetyl, t-butoxycarbonyl, acetylamino, dimethylamino, diethylamino, (1-methylethyl)amino, isopropylamino or aminosulphonyl;

(ii) -(**Q**)-aryl, wherein aryl is optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;

(iii) azetidinyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, morpholinyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, thiomorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, imidazolyl, triazolyl, thienyl, thiazolyl, isoxazolyl, pyridyl, pyrimidinyl, pyrazinyl, tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrolyl, 1,5-dioxa-9-azaspiro[5.5]undecanyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, benzodioxolyl, 2,3-dihydrobenzotriazolyl, 1,2-dihydroquinolinyl or octahydropyrrolo[3,4-c]pyrrolyl;

each of which is optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$; or

(iv) C_{3-7}carbocyclyl, optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;

Yet further preferably $\mathbf{R^8}$ is selected from

(i) phenyl optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ or naphthyl;

(ii) furanyl, tetrahydropyranyl, pyrrolidinyl, piperazinyl, morpholinyl, 1,1-dioxo-thiomorpholinyl, thienyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrolyl, benzodioxolyl, 1,2-dihydroquinolinyl or 2,3-dihydrobenzotriazolyl; each of which is optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;or

(iii) C_{3-7}carbocyclyl (preferably cyclohexyl or cylopentyl, more preferably cyclohexyl) optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;;

Further preferably $\mathbf{R^8}$ is selected from: phenyl, thienyl, pyridyl and benzodioxlyl optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$.

Most preferably $\mathbf{R^8}$ is 1,3 benzodioxolyl.

In another embodiment of the invention $\mathbf{R^8}$ is selected from piperidinyl or piperazinyl, azetidinyl, imidazolyl and thiazolyl, each of which is optionally substituted by up to 3 groups selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$.

In a further embodiment of the invention preferably $\mathbf{R^8}$ is selected from hydrogen, cyano, C_{1-4}alkyl (more preferably methyl), C_{2-6}alkynyl (more prefeably 2-propynyl), hydroxyC_{1-6}alkyl (more preferably hydroxyethyl), C_{1-4}alkoxyC_{1-4}alkyl (more preferably methoxyethyl), haloC_{1-6}alkyl (more preferably fluoroethyl), C_{1-4}alkanoyl (more preferably formyl), C_{1-4}alkoxycarbonyl (more preferably butyloxycarbonyl), N,N-di-C_{1-4}alkylamino (more preferably N,N-dimethylaminoethyl and N,N-dimethylaminopropyl), C_{1-6}alkyl–S(O_n)- (more preferably ethylsulphonyl), cyclopentyl, phenyl, benzyl, cyanophenyl, pyrrolidinyl, pyrrolidinylethyl, imidazolyl, imidazolyC_{1-6}alkyl (more preferably imidazolylethyl), thiazolyl, pyridyl, pyridylC_{1-6}alkyl (more preferably pyridylmethyl) or pyrimidyl wherein a phenyl or heterocyclyl ring is optionally substituted by C_{1-4}alkyl or halo.

When $\mathbf{R^9}$ and/or $\mathbf{R^{10}}$ is a component of group **G**, $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are preferably independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl or $\mathbf{R^9}$ and $\mathbf{R^{10}}$ forms C_{3-7}cycloalkyl or heterocyclyl.

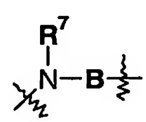
Further preferably hydrogen or C_{1-4}alkyl. Most preferably hydrogen or methyl. Most preferably both $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are methyl.

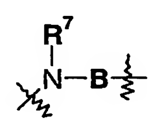
When $\mathbf{R^9}$ and/or $\mathbf{R^{10}}$ is a component of group $\mathbf{R^{18}}$, $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are preferably independently selected from hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl or $\mathbf{R^9}$ and $\mathbf{R^{10}}$ forms C_{3-7}cycloalkyl or heterocyclyl. Further preferably when $\mathbf{R^9}$ is a component of group $\mathbf{R^{18}}$, $\mathbf{R^9}$ is preferably heterocyclyl. Most preferably pyrrolidinyl, 7-azabicyclo[2.2.1]hept-7-yl or. 3-azabicyclo[3.2.2]nonyl.

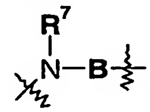
Preferably $\mathbf{R^{17}}$ is hydrogen, hydroxy, cyano or is absent. Most preferably $\mathbf{R^{17}}$ is absent.

Preferably $\mathbf{R^{18}}$ is selected from hydrogen, $\mathbf{R^9}$N($\mathbf{R^{10}}$)C(O)-, $\mathbf{R^9}$C(O)-, $\mathbf{R^9}$OC(O)- or $\mathbf{R^{18a}}$-C($\mathbf{R^9R^{10}}$)- wherein $\mathbf{R^{18a}}$ is $\mathbf{R^9}$N($\mathbf{R^{10}}$)C(O)-. Further preferably $\mathbf{R^9}$C(O)-. Most preferably $\mathbf{R^9}$C(O)- wherein $\mathbf{R^9}$ is heterocyclyl.

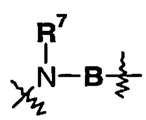
Preferably **A** is selected from a direct bond, optionally substituted C_{1-5}alkylene, carbonyl or -C(O)-C($\mathbf{R^dR^d}$)-, wherein $\mathbf{R^d}$ is independently selected from a direct bond hydrogen and C_{1-2}alkyl. Further preferably **A** is selected from C_{1-5}alkylene optionally substituted with C_{1-4}alkyl, carbonyl or carbonylmethyl. Yet further preferably **A** is a direct bond methylene. Most preferably methylene.

Preferably **B** is selected from optionally substituted C_{1-6}alkylene, optionally substituted C_{3-6}alkenylene, -(C_{1-5}alkyl)$_{\mathbf{aa}}$-O-(C_{1-5}alkyl)$_{\mathbf{bb}}$, -(C_{1-5}alkyl)$_{\mathbf{aa}}$-C(O)-(C_{1-5}alkyl)$_{\mathbf{bb}}$-, -(CH_2)$_{s1}$-C(O)N($\mathbf{R^9}$)-(CH_2)$_{s2}$-, or the group  forms an optionally substituted C_{4-7}heterocyclic ring, wherein **aa** and **bb** are independently 0 to 1 and, wherein the combined length of (C_{1-5}alkyl)$_{\mathbf{aa}}$ and (C_{1-5}alkyl)$_{\mathbf{bb}}$ is less than or equal to C_5alkyl.

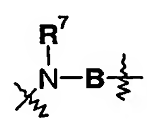
More preferably **B** is C_{1-6}alkylene, C_{3-6}alkenylene ,-(C_{1-5}alkyl)$_{\mathbf{aa}}$-O-(C_{1-5}alkyl)$_{\mathbf{bb}}$-, -(C_{1-5}alkyl)$_{\mathbf{aa}}$-C(O)-(C_{1-5}alkyl)$_{\mathbf{bb}}$-, -(CH_2)$_{s1}$-C(O)N($\mathbf{R^9}$)-, or the group  forms an optionally substituted saturated C_{4-7}heterocyclic ring, wherein **aa** and **bb** are independently 0 or 1 and wherein the combined length of (C_{1-5}alkyl)$_{\mathbf{aa}}$, (C_{1-5}alkyl)$_{\mathbf{bb}}$ is less than or equal to C_5alkyl and wherein C_{1-6}alkylene is optionally substituted by hydroxy.

Further preferably **B** is unsubstituted C_{1-6}alkylene, C_{3-6}alkenylene -$(C_{1-5}alkyl)_{aa}$-O-$(C_{1-5}alkyl)_{bb}$-, -$(C_{1-5}alkyl)_{aa}$-C(O)- or the group  forms an optionally substituted saturated C_{4-7}heterocyclic ring selected from: azetidinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, hexahydrotriazinyl, tetraydrotriazinyl, dihydrotriazinyl, morpholinyl, thiomorpholinyl, thiazinanyl, thiazolidinyl, 1,5-dioxa-9-azaspiro[5.5]undecanyl or octahydropyrrolopyrrolyl, wherein the optional substituents are selected from. cyano, hydroxy, oxo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, $\mathbf{R^9}OC(O)(CH_2)_w$-, $\mathbf{R^9R^{10}}NC(O)(CH_2)_w$- or halo, wherein **w** is an integer between 0 and 4 and $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are as defined above. Further preferably the optional substituents are selected from: cyano, hydroxy, oxo, C_{1-4}alkyl, C_{1-4}alkoxy and C_{1-4}alkanoyl, **aa** and **bb** are independently 0 or 1, wherein the combined length of $(C_{1-5}alkyl)_{aa}$ and $(C_{1-5}alkyl)_{bb}$ is less than or equal to C_5alkyl and wherein C_{1-6}alkylene is optionally substituted by hydroxy.

Yet further preferably **B** is selected from: methylene, ethylene, propylene, propyl-2-ene, butylene, pentylene, 2-propenyl, propoxy, ethoxyethyl, methylcarbonyl or methylcarbonylamino.

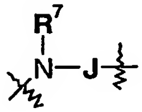
or the group  forms an C_{4-7}heterocyclic ring selected from:pyrrolidinyl, piperidinyl, or piperazinyl, wherein the optional substituents are selected from oxo.

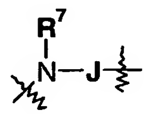
Most preferably **B** is selected from ethylene or butylene.

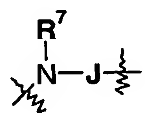
In another embodiment of the invention preferably **B** is selected from optionally substituted C_{1-6}alkylene or the group  forms a C_{5-7}heterocyclic ring. Preferably unsubstituted C_{-6}alkylene or a C_{5-7}heterocyclic saturated ring. Most preferably methylene, ethylene, propylene, butylene or piperazinyl.

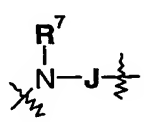
Peferably **G** is a direct bond, -O- or –C($\mathbf{R^9R^{10}}$)-. More preferably –C($\mathbf{R^9R^{10}}$)-. Most preferably –C$(CH_3)_2$-.

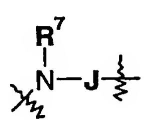
Preferably **M** is –CH_2-O-.

When R^3 is selected from a group of Formula (IIc) or Formula (IId) then the group  preferably forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms.

More preferably the group  forms an optionally substituted saturated C_{4-7}heteocyclic ring.

Further preferably the group  forms an optionally substituted saturated C_{4-7}heteocyclic ring selected from: azetidinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, hexahydrotriazinyl, tetraydrotriazinyl, dihydrotriazinyl, morpholinyl, thiomorpholinyl, thiazinanyl, thiazolidinyl or octahydropyrrolopyrrolyl, wherein the optional substituents are selected from oxo.

Further preferably the group  forms an optionally substituted saturated C_{4-7}heteocyclic ring selected from: pyrrolidinyl, piperidinyl or piperazinyl, wherein the optional substituents are selected from oxo.

Most preferably the group  forms an optionally substituted saturated C_{4-7}heteocyclic ring selected from: piperazinyl.

Preferably **K** is selected from: $-(CH_2)_s-$, $-(CH_2)_s-O-(CH_2)_s-$, $-(CH_2)_s-C(O)-(CH_2)_s-$, $-(CH_2)_s-N(\mathbf{R}^{18})-(CH_2)_s-$, $-(CH_2)_s-C(O)N(\mathbf{R}^{18})-(CH_2)_s-$, $-(CH_2)_s-N(\mathbf{R}^{18})C(O)-(CH_2)_s-$, $-(CH_2)_s-S(O)_2N(\mathbf{R}^{18})-(CH_2)_s-$, or $-(CH_2)_s-NHS(O)_2-(CH_2)_s-$, wherein s is independently selected from 0,1,2,3 or 4, $\mathbf{R}^{18}$ is selected from hydrogen or C_{1-4}alkyl (preferably hydrogen) and the $-(CH_2)_s-$ group is optionally substituted by hydroxy or C_{1-4}alkyl.

More preferably **K** is selected from: $-(CH_2)_s-$, $-(CH_2)_s-O-(CH_2)_s-$, $-(CH_2)_s-C(O)-$, $-C(O)-(CH_2)_s-$, $-(CH_2)_s-N(\mathbf{R^{18}})-$, $-(CH_2)_s-C(O)N(\mathbf{R^{18}})-$, $-(CH_2)_s-N(\mathbf{R^{18}})C(O)-(CH_2)_s-$, $-(CH_2)_s-S(O)_2N(\mathbf{R^{18}})-$ or $-(CH_2)_s-NHS(O)_2-$,
wherein s is independently selected from 0,1,2,3 or 4, $\mathbf{R^{18}}$ is selected from hydrogen or C_{1-4}alkyl (preferably hydrogen or methyl) and the $-(CH_2)_s-$ group is optionally substituted by hydroxy or C_{1-4}alkyl.

More preferably **K** is selected from: methylene, ethylene, propylene, butylene, oxy, 2-hydroxypropylene, carbonyl, methylcarbonyl, ethylcarbonyl, (methyl)methylcarbonyl, (ethyl)methylcarbonyl, carbonylmethylene, carbonylethylene, ethoxyethylene, amino, 2-hydroxypropylamino, carbonylamino, methylcarbonylamino, N-methyl-methylcarbonylamino, aminocarbonyl, methylaminocarbonyl, methylaminocarbonylmethyl, propylsulphonylamino or methylaminosulphonyl.

Further preferably **K** is selected from: methylene, ethylene, propylene, butylene carbonyl, methylcarbonyl or N-methylmethylcarbonylamino.

Most preferably **K** is selected from: methylcarbonyl and N-methylmehtylcarbonylamino.

Preferably optional substituents on heterocyclyl groups in $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ or on heterocyclyl groups formed when $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ together form a heterocyclic ring are selected from: optionally substituted C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $\mathbf{R^9}O(CH_2)_p-$, $\mathbf{R^9}C(O)O(CH_2)_w-$, $\mathbf{R^9}OC(O)(CH_2)_w-$, $\mathbf{R^{16}}S(O_n)(CH_2)_w-$, $\mathbf{R^9}\mathbf{R^{10}}NC(O)(CH_2)_w-$ or halo; wherein w is an integer between 0 and 4 and **p**, $\mathbf{R^9}$, $\mathbf{R^{10}}$ and $\mathbf{R^{16}}$ are as defined above.

More preferably optional substituents on $\mathbf{R^8}$ are selected from: cyano, hydroxy, oxo, nitro, halo, trifluromethyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, $\mathbf{R^9}OC(O)(CH_2)_w-$, $\mathbf{R^9}\mathbf{R^{10}}N(CH_2)_w-$, $\mathbf{R^9}\mathbf{R^{10}}NC(O)(CH_2)_w-$, $\mathbf{R^9}\mathbf{R^{10}}NC(O)(CH_2)_w-$, $\mathbf{R^9}\mathbf{R^{10}}NC(O)N(\mathbf{R^9})(CH_2)_w-$, $\mathbf{R^9}OC(O)N(\mathbf{R^9})(CH_2)_w-$, or halo, wherein w is an integer between 0 and 4 and $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are selected from: hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulphonyl and C_{3-7}carbocyclyl.

Further preferably optional substituents on $\mathbf{R^8}$ are selected from: cyano, hydroxy, oxo, amino, N,N-diC_{1-4}alkyamino, N,N-diC_{1-4}alkyaminoC_{1-4}alkyl, N'-C_{1-4}alkylureido, N-C_{1-4}alkylsulphonylamino, N,N-di-C_{1-4}alkylsulphonylamino, nitro, halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C1-4alkoxycarbonylamino and C_{3-7}carbocyclylcarbonylamino.

More preferably optional substituents on $\mathbf{R^8}$ are selected from: cyano, oxo, methyl, *t*-butyl, methoxy, acetyl, amino, N,N-dimethylamino, N'-isopropylureido, N'-cyclohexylureido, N-methylsulphonylamino, N,N-dimethylsulphonylamino, nitro, chloro, fluoro, trifluoromethyl, isopropoxycarbonylamino and cyclopentylcarbonylamino.

Most preferably op tional substituents on $\mathbf{R^8}$ are selected from: methoxy, fluoro, methylsulphonylamino and isopropoxycarbonylamino.

In a further embodiment of the invention optional substituents on $\mathbf{R^8}$ are selected from: C_{1-4}alkoxy, fluoro, C_{1-4}alkylsulphonylamino, C_{1-4}alkanoylamino, C_{1-4}alkylureido and C_{1-4}alkoxycarbonylamino.

In a further embodiment of the invention when $\mathbf{R^8}$ is phenyl then $\mathbf{R^8}$ is preferably substituted and when $\mathbf{R^8}$ is a heterocyclic ring $\mathbf{R^8}$ is preferably unsubstituted.

Preferably the optional substituents on alkyl, alkenyl, alkynyl, cycloalkyl and aryl groups are independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, hydroxy, oxo, cyano, C_{1-6}alkoxy, halo (preferably fluoro), $\mathbf{R^{16}}S(O_n)(CH_2)_w$-, $\mathbf{R^9}OC(O)$-, optionally substituted arylC_{1-3}alkoxy wherein $\mathbf{R^9}$ is as defined above.

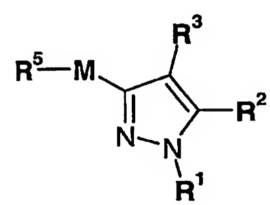
Preferably the optional substituents on optionally substituted aryl and arylC_{1-6}alkyl groups are selected from: optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, halo (preferably fluoro), C_{1-3}perfluoroalkyl, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $\mathbf{R^9}O(CH_2)_p$-, $\mathbf{R^9}C(O)O(CH_2)_w$-, $\mathbf{R^9}OC(O)(CH_2)_w$-, $\mathbf{R^{16}}S(O_n)(CH_2)_w$-, $\mathbf{R^9R^{10}}NC(O)(CH_2)_w$- or halo; wherein **w** is an integer between 0 and 4 and **n**, $\mathbf{R^9}$ and $\mathbf{R^{10}}$ are as defined above.

In preferences for heterocyclyl in $\mathbf{R^8}$ the nitrogen atoms contained in $\mathbf{R^8}$ heteroaromatic rings exist either as drawn or, where chemically allowed, in their oxidised (N→O, N-OH) state.

Where optional substitution is mentioned at various places the optional substituents also comprise the following definition which refers to one, two, three or more optional substituents. Unless otherwise indicated above (i.e., where a list of optional substituents is specifically listed within a definition), each substituent can be independently selected from C_{1-8}alkyl (eg, C_{2-6}alkyl, and most preferably methyl, ethyl or *tert*-butyl); C_{3-8}cycloalkoxy, preferably cyclopropoxy, cyclobutoxy or cyclopentoxy; C_{1-6}alkoxy, preferably methoxy or C_{2-4}alkoxy; halo, preferably Cl or F; Hal_3C-, Hal_2CH-, $HalCH_2$-, Hal_3CO-, Hal_2CHO or Hal CH_2O, wherein Hal represents halo (preferably F); $\mathbf{R^g}CH_2O$-, $\mathbf{R^h}C(O)N(\mathbf{R})$-, $\mathbf{R^h}SO_2N(\mathbf{R})$- or

R^g-R^hN-, wherein R^g and R^h independently represent hydrogen or C_{1-8}alkyl (preferably methyl or C_{2-6}alkyl or C_{2-4}alkyl), or R^g-R^hN- represents an optionally substituted C_{3-8}, preferably C_{3-6}, heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; hydrogen; or R^kC(O)O- or R^kC(O)-, R^k representing hydrogen, optionally substituted phenyl or C_{1-6}alkyl (preferably methyl, ethyl, *iso*-propyl or *tert*-butyl). For optional substitution of the heterocyclic ring represented by R^g-R^hN-, at least one (eg, one, two or three) substituents may be provided independently selected from C_{1-6}alkyl (eg, C_{2-4}alkyl, more preferably methyl); phenyl; CF_3O-; F_2CHO-; C_{1-8}alkoxy, preferably methoxy, ethoxy or C_{3-6}alkoxy; C_{1-8}alkoxyC(O), preferably methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl or C_{3-6}alkoxyC(O)-; phenoxycarbonyl; phenoxy; C_{1-8}alkanoyl, preferably acetyl, ethanoyl or C_{3-6}alkyanoyl; carboxy; C_{1-8}alkylS(O_{nn}) wherein **nn** is an integer between 0 and 2, preferably methylthio, ethylthio, C_{3-6}alkylthio, methylsulphinyl, ethylsulphinyl, C_{3-6}alkylsulphinyl, methylsulphonyl, ethylsulphonyl or C_{3-6}alkylsulphonyl; hydroxy; halo (eg, F, Cl or Br); $R^m$$R^n$N- where R^m and R^n are independently hydrogen or C_{1-6}alkyl (preferably C_{2-4}alkyl, more preferably methyl, most preferably R^m=R^n=methyl); and nitro.

According to a further aspect of the invention there is provided a compound of Formula (Ib)



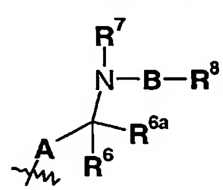
Formula (Ib)

wherein:

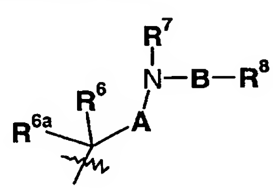
R^1 represents hydrogen or unsubstituted C_{1-6}alkyl;

R^2 represents optionally substituted phenyl;

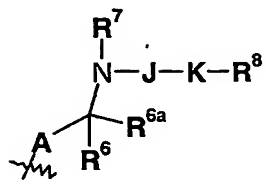
R^3 is selected from a group of Formula (IIa) to Formula (IId):



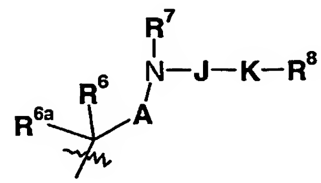
Formula (IIa)



Formula (IIb)

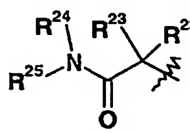


Formula (IIc)

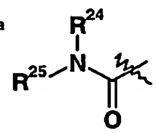


Formula (IId)

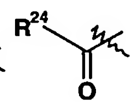
R^5 is selected from a one of a group of Formula **III-a** to **III-l**:



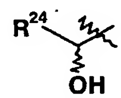
III-a



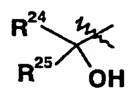
III-b



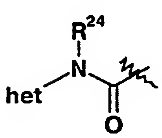
III-c



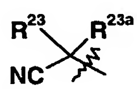
III-d



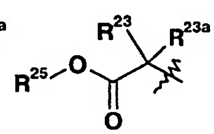
III-e



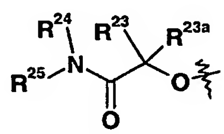
III-f



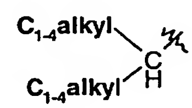
III-g



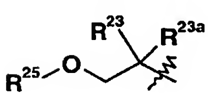
III-h



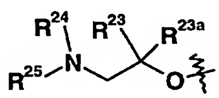
III-i



III-j



III-k



III-l

;

wherein:

het represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

$\mathbf{R^{23}}$ and $\mathbf{R^{23a}}$ are independently selected from:

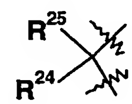
(i) hydrogen or optionally substituted C_{1-8}alkyl; or

(ii) $\mathbf{R^{23}}$ and $\mathbf{R^{23a}}$ together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

$\mathbf{R^{24}}$ and $\mathbf{R^{25}}$ are selected from:

(i) $\mathbf{R^{24}}$ selected from hydrogen; optionally substituted C_{1-8}alkyl; optionally substituted aryl; -$\mathbf{R^d}$-Ar, where $\mathbf{R^d}$ represents C_{1-8}alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and $\mathbf{R^{25}}$ is selected from hydrogen; optionally substituted C_{1-8}alkyl and optionally substituted aryl;

(ii) wherein the group of Formula (III) represents a group of Formula **III-a**, **III-b** or **III-i**, then the group $NR^{24}(-R^{25})$ represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

(iii) wherein the group of Formula (III) represents structure **III-e**,  represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

$\mathbf{R^6}$ **and** $\mathbf{R^{6a}}$ are independently selected from hydrogen, fluoro or optionally substituted C_{1-6}alkyl.

$\mathbf{R^7}$ is selected from: hydrogen or C_{1-4}alkyl;

$\mathbf{R^8}$ is selected from

(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, haloC_{1-6}alkyl, hydroxy, cyano, C_{1-6}alkyl$S(O_n)$-, -O-$\mathbf{R^b}$, C_{1-4}alkoxyC_{1-4}alkyl, -C(O)-$\mathbf{R^b}$, C(O)O-$\mathbf{R^b}$, -NH-C(O)-$\mathbf{R^b}$, N,N-di-C_{1-4}alkylamino or -$S(O_n)NR^bR^c$ where $\mathbf{R^b}$ and $\mathbf{R^c}$ are independently selected from hydrogen and C_{1-6}alkyl, and **n** is 0, 1 or 2;

(ii)–aryl, , optionally substituted by up to 4 substituents selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;

(iii) C_{4-7}heterocyclyl, optionally substituted by up to 4 substituents selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$; or

(iv) C_{3-7}carbocyclyl, , optionally substituted by up to 4 substituents selected from $\mathbf{R^{12}}$, $\mathbf{R^{13}}$ and $\mathbf{R^{14}}$;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently selected from: hydrogen, hydroxy, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclylC_{1-6}alkyl or $\mathbf{R^9}$ and $\mathbf{R^{10}}$ taken together can form an optionally substituted ring of 3-9 atoms or $\mathbf{R^9}$ and $\mathbf{R^{10}}$ taken together with the carbon atom to which they are attached form a carbonyl group;

$\mathbf{R^{12}}$ is selected from: hydrogen, hydroxy, $R^{17}R^{18}N(CH_2)_{cc}$-, $R^{17}R^{18}NC(O)(CH_2)_{cc}$-, optionally substituted C_{1-6}alkyl- $C(O)N(R^9)(CH_2)_{cc}$-, optionally substituted C_{1-6}alkyl-$SO_2N(R^9)$-, optionally substituted aryl-$SO_2N(R^9)$-, C_{1-3}perfluoroalkyl-$SO_2N(R^9)$-; optionally substituted C_{1-6}alkyl-$N(R^9)SO_2$-, optionally

substituted aryl-N(R^9)SO_2-, C_{1-3}perfluoroalkyl-N(R^9)SO_2- optionally substituted C_{1-6}alkanoyl-N(R^9)SO_2-; optionally substituted aryl-C(O)N(R^9)SO_2-, optionally substituted C_{1-6}alkyl-S(O_n) -, optionally substituted aryl-S(O_n) - , C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted C_{1-6}alkoxy, carboxy, halo, nitro or cyano;

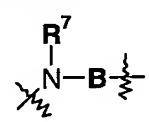
R^{13} and **R^{14}** are independently selected from: hydrogen, hydroxy, oxo, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkanoyl, optionally substituted C_{2-6}alkenyl, cyano, nitro, C_{1-3}perfluoroalkyl-, C_{1-3}perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, $R^9O(CH_2)_s$-, $R^9(O)O(CH_2)_s$-, $R^9OC(O)(CH_2)_s$-, $R^{16}S(O_n)(CH_2)_s$-, $R^9R^{10}NC(O)(CH_2)_s$- or halo;**A** is selected from optionally substituted C_{1-5}alkylene, carbonyl or -C(O)-C(R^dR^d)-, wherein R^d is independently selected from hydrogen and C_{1-2}alkyl.;

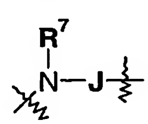
R^{17} is independently selected from: hydrogen, hydroxy, cyano or optionally substituted C_{1-6}alkyl;

R^{18} is a group of formula R^{18a}-C(R^9R^{10})$_{0-1}$- wherein R^{18a} is selected from: $R^{19}OC(O)$-, $R^9R^{10}NC(O)$-, $R^9R^{10}N$-, $R^9C(O)$-, $R^9C(O)N(R^{10})$-, $R^9R^{10}NC(O)$-, $R^9R^{10}NC(O)N(R^{10})$-, $R^9SO_2N(R^{10})$-, $R^9R^{10}NSO_2N(R^{10})$-, $R^9C(O)O$-, $R^9OC(O)$-, $R^9R^{10}NC(O)O$-, R^9O-, $R^9S(O_n)$-, $R^9R^{10}NS(O_n)$ -, hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted heterocyclyl;

or R^{17} and R^{18} when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;

R^{19} is selected from: hydrogen, optionally substituted C_{1-6}alky, optionally substituted aryl, optionally substituted arylC_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclylC_{1-6}alkyl;

B is selected from optionally substituted C_{1-6}alkylene or the group  forms an optionally substituted C_{4-7}heterocyclic ring, wherein the optional substituents are selected from R^{12}, R^{13} and R^{14};

the group  preferably forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, wherein the optional substituents are selected from R^{12}, R^{13} and R^{14};

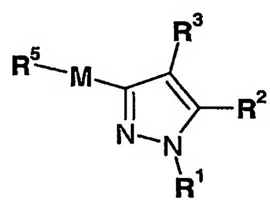
K is selected from: a direct bond, $-(CH_2)_{s1}-$, $-(CH_2)_{s2}-O-(CH_2)_s-$, $-(CH_2)_{s1}-C(O)-(CH_2)_{s2}-$, $-(CH_2)_{s1}-S(O_n)-(CH_2)_{s2}-$, $-(CH_2)_{s1}-N(\mathbf{R^{18}})-(CH_2)_{s2}-$, $-(CH_2)_{s1}-C(O)N(\mathbf{R^9})-(CH_2)_{s2}-$, $-(CH_2)_{s1}-N(\mathbf{R^9})C(O)-(CH_2)_{s2}-$, $-(CH_2)_{s1}-N(\mathbf{R^9})C(O)N(\mathbf{R^9})-(CH_2)_{s2}-$, $-(CH_2)_{s1}-OC(O)-(CH_2)_{s2}-$, $-(CH_2)_{s1}-C(O)O-(CH_2)_{s2}-$, $-(CH_2)_{s1}-N(\mathbf{R^9})C(O)O-(CH_2)_{s2}-$, $-(CH_2)_{s1}-OC(O)N(\mathbf{R^9})-(CH_2)_{s2}-$, $-(CH_2)_{s1}-OS(O_n)-(CH_2)_{s2}-$, or $-(CH_2)_{s1}-S(O_n)-O-(CH_2)_{s2}-$, $-(CH_2)_{s1}-S(O)_2N(\mathbf{R^9})-(CH_2)_{s2}-$, $-(CH_2)_{s1}-N(\mathbf{R^9})S(O)_2-(CH_2)_{s2}-$; wherein the $-(CH_2)_{s1}-$ and $-(CH_2)_{s2}-$ groups are independently optionally substituted by hydroxy, fluoro, cyano, carbamoyl, C_{1-4}alkyl and C_{1-4}alkoxy,

n is an integer from 0 to 2;

s1 and **s2** are independently selected from an integer from 0 to 4, and **s1+s2** is less than or equal to 4;

or a salt, pro-drug or solvate thereof.

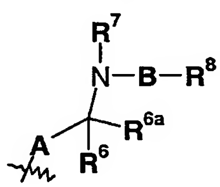
According to a further aspect of the invention there is provided a compound of Formula (Ic)



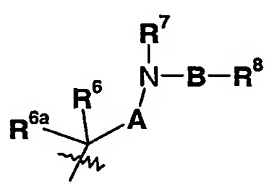
Formula (Ic)

wherein

$\mathbf{R^3}$ is selected from a group of Formula (IIa) or Formula (IIb):



Formula (IIa)



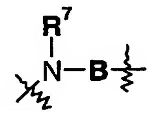
Formula (IIb)

and $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^{6a}}$, $\mathbf{R^7}$, $\mathbf{R^8}$, **A**, **B** and **M** are as defined above;

or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ic), wherein:

A is optionally substituted C_{1-5}alkylene;

B is selected from optionally substituted $C_{1\text{-}6}$alkylene or the group  forms a ring containing $C_{5\text{-}7}$heterocyclic ring;

M is $-CH_2$-O-;

$\mathbf{R^1}$ is hydrogen or $C_{1\text{-}4}$alkyl;

$\mathbf{R^6}$ and $\mathbf{R^{6a}}$, are independently selected from hydrogen and optionally substituted $C_{1\text{-}6}$alkyl;

$\mathbf{R^7}$ is selected from: hydrogen or $C_{1\text{-}4}$alkyl;

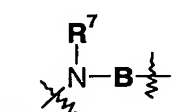
$\mathbf{R^8}$ is selected from hydrogen, cyano, $C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkynyl, $C_{1\text{-}6}$alkanoyl, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkyl, $C_{1\text{-}6}$alkoxycarbonyl, N,N-di-$C_{1\text{-}4}$alkylamino, aryl, aryl$C_{1\text{-}6}$alkyl, $C_{3\text{-}7}$cycloalkyl, $C_{3\text{-}7}$cycloalkyl$C_{1\text{-}6}$alkyl, heterocyclyl, heterocyclyl$C_{1\text{-}6}$alkyl, or heterocyclylcarbonyl$C_{1\text{-}4}$alkyl wherein aryl and heterocyclyl rings are optionally substituted by cyano and $C_{1\text{-}4}$alkyl; and

$\mathbf{R^2}$ and $\mathbf{R^5}$; are as defined above

or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ic), wherein:

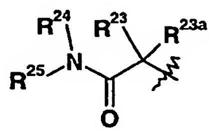
A is optionally substituted $C_{1\text{-}5}$alkylene;

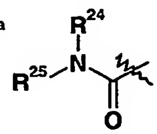
B is selected from optionally substituted $C_{1\text{-}6}$alkylene or the group  forms a ring containing $C_{5\text{-}7}$heterocyclic ring;

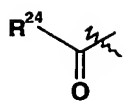
$\mathbf{R^1}$ is hydrogen or $C_{1\text{-}4}$alkyl, preferably hydrogen;

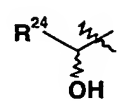
$\mathbf{R^2}$ is an optionally substituted monocyclic aromatic ring structure, preferably optionally substituted phenyl, most preferably 3,5-dimethylphen-1-yl;

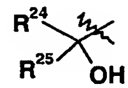
$\mathbf{R^5}$ is a group of Formula (III) wherein the group of Formula (III) is selected from a group of Formula **III-a**; **III-b**; **III-c**; **III-d**; **III-e**; **III-f**, **III-g** , **III-h**, **III-I**, **III-j**, **III-k** and **III-l**;

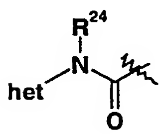

III-a

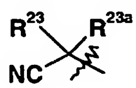

III-b

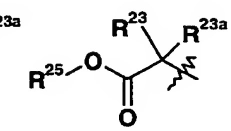

III-c

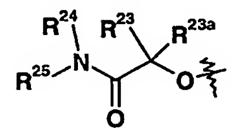

III-d

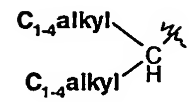

III-e

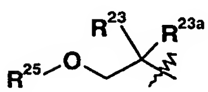

III-f

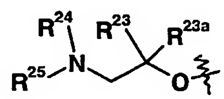

III-g


III-h


III-i


III-j


III-k


III-l

wherein $\mathbf{R}^{23}$, $\mathbf{R}^{23a}$, $\mathbf{R}^{24}$ and $\mathbf{R}^{25}$ are as defined above, preferably the group of Formula (III) is selected from (III-a), (III-g) and (III-h);

$\mathbf{R}^{6}$and $\mathbf{R}^{6a}$, are independently selected from hydrogen and optionally substituted C_{1-6}alkyl;

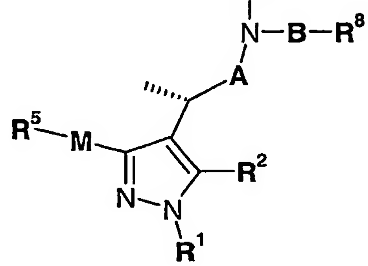
$\mathbf{R}^{7}$ is selected from: hydrogen or C_{1-4}alkyl;

$\mathbf{R}^{8}$ is selected from hydrogen, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-6}alkoxycarbonyl, N,N-di-C_{1-4}alkylamino, aryl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, or heterocyclylcarbonylC_{1-4}alkyl wherein aryl and heterocyclyl rings are optionally substituted by cyano and C_{1-4}alkyl; and

$\mathbf{R}^{2}$, and $\mathbf{R}^{5}$; are as defined above

or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Id):



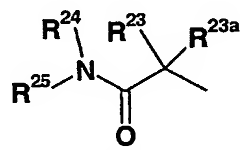
Formula (Id)

Wherein R^1, R^2, R^5; R^7, R^8, A, B and M are as defined above

or salt, solvate or pro-drug thereof.

A yet further preferred group of compounds of the invention comprises a compound of Formula (Ib), (Ic) or (Id) wherein:

R^5 is a group of Formula (III) wherein the group of Formula (III) is a group of formula **IIIa**:



IIIa ;

wherein R^{23}, R^{23a}, R^{24} and R^{25} are as defined above;

or a salt, pro-drug or solvate thereof.

According to a further aspect of the invention there is provided a compound of Formula (I) or Formula (Ia), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIc) or Formula (IId) and R^1, R^2 and R^5 are as defined above.

According to a further aspect of the invention there is provided a compound of Formula (I) or Formula (Ia), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIe) or Formula (IIf) and R^1, R^2 and R^5 are as defined above.

According to a further aspect of the invention there is provided a compound of Formula (I) or Formula (Ia), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIa), Formula (IIc) or Formula (IIe) and R^1, R^2 and R^5 are as defined above.

According to a further aspect of the invention there is provided a compound of Formula (I) or Formula (Ia), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIb), Formula (IId) or Formula (IIf) and R^1, R^2 and R^5 are as defined above.

Particularly preferred compounds according to the present invention are wherein the compound is selected from:

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-pyrid-4-ylethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-pyrid-4-ylbutyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[4-(4-methoxyphenyl)butyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-phenylethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(43-trifluoromethylphenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-fluorophenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(3-fluorophenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(3-methoxyphenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-methoxyphenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(3,4-difluorophenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-isopropylureidophenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-{cyclopentylcarbonylamino}phenyl)ethyl]-(2S)-propylamine;

[2-(4-methylsulphonylaminophenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-{isopropoxycarbonylamino}phenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-{cyclohexylureido}phenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)ethyl]-(2S)-propylamine;

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.2]oct-2-yl)propoxy]-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(3-methoxyphenyl)ethyl]-(2S)-propylamine; and

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.2]oct-2-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine;

or a salt, pro-drug or solvate thereof.

More particularly preferred compounds according to the present invention are wherein the compound is selected from:

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-pyrid-4-ylethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-pyrid-4-ylbutyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[4-(4-methoxyphenyl)butyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(43-trifluoromethylphenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-fluorophenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(3-methoxyphenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-methoxyphenyl)ethyl]-(2S)-propylamine;

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(4-methylsulphonylaminophenyl)ethyl]-(2S)-propylamine; and

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.2]oct-2-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine;

or a salt, pro-drug or solvate thereof.

Most preferred compounds according to the present invention are wherein the compound is selected from:

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine; and

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.2]oct-2-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine;

or a salt, pro-drug or solvate thereof.

In another embodiment of the invention preferred compounds according to the present invention are wherein the compound is selected from:

2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-(2-pyridin-4-ylethyl)ethanamine;

2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-(2-pyridin-4-ylbutyl)ethanamine;

2-[3-(2,2-dimethyl-3-oxo-3-(7-azabicyclo[2.2.1]hept-7-yl)propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-(2-pyridin-4-ylethyl)ethanamine; and

2-[3-(2,2-dimethyl-3-oxo-3-(7-azabicyclo[2.2.1]hept-7-yl)propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-(2-pyridin-4-ylbutyl)ethanamine;

or a salt, pro-drug or solvate thereof.

The compounds of Formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the Formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the Formula (I). Various forms of pro-drugs are known in the art. For examples of such pro-drug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters.

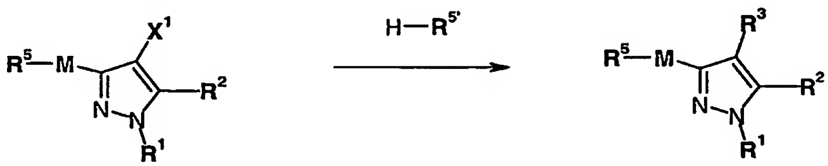
An in-vivo hydrolysable ester of a compound of the Formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an

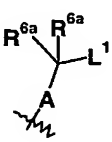
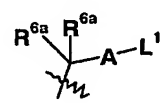
organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

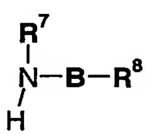
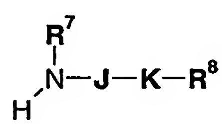
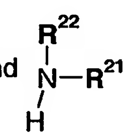
The compounds of Formula (I) can be prepared by a process comprising a step selected from (a) to (h) as follows, these processes are provided as a further feature of the invention:-

(a) Reaction of a compound of formula **XXXII** with a compound of formula $\mathbf{L^2\text{-}R^{5'}}$ to form a compound of Formula (I),

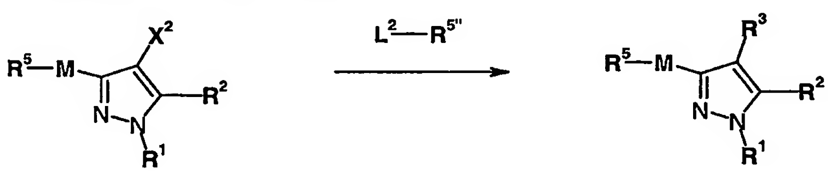


XXXII **Formula (I)**

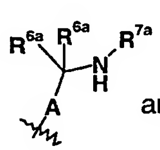
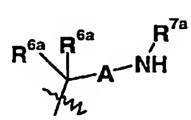
wherein $\mathbf{X^1}$ is selected from:  and  ; $\mathbf{L^1}$ is a displaceable group; and

$\mathbf{H\text{-}R^{5'}}$ is selected from:  ,  and  ;

(b) Reaction of a compound of formula **XXXIII** with a compound of formula $\mathbf{H\text{-}R^{5''}}$ to form a compound of Formula (I),



XXXIII **Formula (I)**

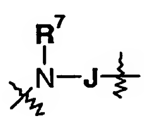
wherein $\mathbf{X^2}$ is selected from:  and  ; $\mathbf{L^2}$ is a displaceable group and $\mathbf{R^{7a}}$ is selected from the definition of $\mathbf{R^7}$ or $\mathbf{R^{22}}$ above, and

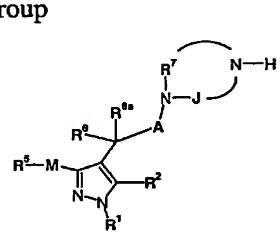
L^2-$R^{5''}$ is selected from: $L^2—B—R^8$, $L^2—J—K—R^8$ and $L^2—R^{21}$

(c) For compounds of Formula (I) wherein R^3 is a group of Formula (IIa), (IIb), (IIc) or (IId) and R^7 is other than part of a heterocyclic ring or hydrogen, reaction of a compound of Formula (I) wherein R^3 is a group of Formula (IIa), (IIb), (IIc) or (IId) and R^7 is hydrogen with a group of formula L^3-R^{7a}, wherein R^{7a} is as defined above for R^7 with the exclusion of hydrogen and L^3 is a displaceable group;

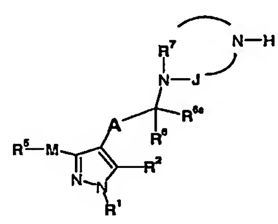
(d) For compounds of Formula (I) wherein R^3 is a group of Formula (IIe) or (IIf) and R^{21} is other than hydrogen, reaction of a compound of Formula (I) wherein R^3 is a group of Formula (IIe) or (IIf) and R^{21} is hydrogen with a group of formula L^4-R^{21a}, wherein R^{21a} is as defined above for R^{21} with the exclusion of hydrogen and L^4 is a displaceable group;

(e) For compounds of Formula (I) wherein R^3 is a group of Formula (IIe) or (IIf) and R^{22} is other than hydrogen, reaction of a compound of Formula (I) wherein R^3 is a group of Formula (IIe) or (IIf) and R^{22} is hydrogen with a group of formula L^5-R^{22a}, wherein R^{22a} is as defined above for R^{22} with the exclusion of hydrogen and L^5 is a displaceable group;

(f) For compounds of Formula (I) wherein R^3 is a group of Formula (IIc) or (IId) and the group  together forms an optionally substituted nitrogen-containing heterocyclic ring containing 4-7 carbons atoms, reaction of a compound of Formula **XXXIVa** or **XXXIVb**, with a compound of Formula L^6-K-R^8, wherein L^6 is a displaceable group

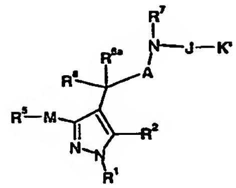


XXXIVa

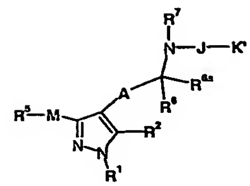


XXXIVb

(g) For compounds of Formula (I) wherein R^3 is a group of Formula (IIc) or (IId), reaction of a compound of Formula **XXXVa** or **XXXVb**, with a compound of Formula L^7-K''-R^8, wherein L^7 is a displaceable group, and wherein the groups K' and K'' comprise groups which when reacted together form K,

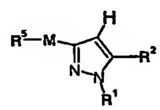


XXXVa



XXXVb ;

(h) reaction of a compound of Formula **XXXVI** with an electrophillic compound of the formula $\mathbf{L^8}$-$\mathbf{R^5}$, wherein $\mathbf{L^8}$ is a displaceable group



XXXVI

and thereafter if necessary:

i) converting a compound of the Formula (I) into another compound of the Formula (I);

ii) removing any protecting groups;

iii) forming a salt, pro-drug or solvate.

Specific reaction conditions for the above reations are as follows:

Process a) Compounds of formula **XXXII** and H-$\mathbf{R^{5'}}$ can be coupled together in the presence of an organic base (such as DIPEA [di-isopropylethylamine]) or an inorganic base (such as potassium carbonate) base, in a suitable solvent such as DMA or DMF, at a temperature from room temperature and 120°C. Suitable displaceable groups include: a halide, such as chloro, or a methane sulphonate or toluene sulphonate;

Process b) Compounds of **XXXIII** and $\mathbf{L^2}$-$\mathbf{R^{5''}}$ can be coupled together in the presence of an organic base(such as DIPEA) or an inorganic base (such as potassium carbonate), in a suitable solvent such as DMA or DMF, at a temperature from room temperature to 120°C. Suitable displaceable groups include: a halide, such as chloro, or a methane sulphonate or toluene sulphonate,

alternatively if $\mathbf{L^2}$ is a hydroxy group then the $\mathbf{L^2}$-$\mathbf{R^{5''}}$;can be reacted with a compound of formula **XXXIII** under Mitsunobu reaction conditions;

Process c, d, e and f) Reaction conditions to facilitate these reactions can be using (i) alkylation reaction conditions or (ii) acylation reaction conditions: Examples of said conditions include:

(i) alkylation reaction conditions - the presence of an organic base(such as DIPEA) or an inorganic base (such as potassium carbonate), in a suitable solvent such as DMF, DMA,

DCM, at a temperature from room temperature to 120°C. Suitable displaceable groups include: a halide, such as chloro, methane sulphonate or toluene sulphonate;

(ii) acylation reaction conditions - presence of organic base, such as triethylamine, temperature 0°C to 50-60°C in a suitable solvent such as DCM. Suitable displaceable groups include an acylchloride or an acid anhydride,

Process g) The skilled man would be familiar with a variety of reaction conditions and values for **K'** and **K''**, which when reacted together would form the group **K**, examples of said conditions and values for **K'** and **K''** include:

(i.) *For compounds of Formula (I) where K is* $-(CH_2)_{s1}-N(R^9)C(O)-(CH_2)_{s2}-$ these can be prepared by reacting a compound where **K'** is $-(CH_2)_{s1}-N(\mathbf{R}^9)H$ with a carboxylic acid for formula $HOOC-(CH_2)_{s2}-\mathbf{R}^8$ to form the amide. Coupling of amino groups with carboxylic acids are well known in the art and can be facilitated by a number of chemical reactions using an appropriate coupling reagent. For example a carbodiimide coupling reaction can be performed with EDCl in the presence of DMAP in a suitable solvent such as DCM, chloroform or DMF at room temperature;

(ii.) *For compounds of Formula (I) where K is* $-(CH_2)_{s1}-C(O)N(R^9)-(CH_2)_{s2}-$ *these can be prepared by* reacting a compound where **K'** is $-(CH_2)_{s1}-COOH$ with an amine of the $HN(\mathbf{R}^9)-(CH_2)_{s2}-\mathbf{R}^8$ to form the amide. Methodology is identical to processes described in (i) above in this section;

(iii.) *For compounds of Formula (I) where K is* $-(CH_2)_{s1}-N(R^9)C(O)O-(CH_2)_{s2}-$ these can be prepared by reacting a compound where **K'** is $-(CH_2)_{s1}-N(\mathbf{R}^9)H$ with a chloroformate of formula $ClC(O)O--(CH_2)_{s2}-\mathbf{R}^8$ in a suitable solvent, such as DCM or chloroform, in the presence of a base, such as *N*-methylmorpholine, pyridine or triethylamine, at a temperature between -10°C and 0°C;

(iv.) *For compounds of Formula (I) where K is* $-(CH_2)_{s1}-OC(O)N(R^9-(CH_2)_{s2}-$ these can be prepared by reacting a compound where **K'** is $-(CH_2)_{s1}-OC(O)Cl$ with a compound of formula $HN(\mathbf{R}^9)-(CH_2)_{s2}-\mathbf{R}^8$. Methodology is identical to processes described in (iii) above in this section;

(v.) *For compounds of Formula (I) where K is* $-(CH_2)_{s1}-N(R^9)S(O_2)-(CH_2)_{s2}-$ these can be prepared by reacting a compound where **K'** is $-(CH_2)_{s1}-N(\mathbf{R}^9)H$ with a sulphonyl chloride of formula $ClS(O_2)-(CH_2)_{s2}-\mathbf{R}^8$ in the presence of a base, such as

triethylamine or pyridine, in a suitable solvent such as chloroform or DCM at a temperature between 0°C and room temperature;

(vi.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$-S(O_2)N(R^9) -$(CH_2)_{s2}$-*
these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-S(O2)Cl with a compound of HN($\mathbf{R^9}$)-$(CH_2)_{s2}$-$\mathbf{R^8}$. Methodology is identical to processes described in (v) above in this section

(vii.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$- N(R^9) -$(CH_2)_{s2}$-*
these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-$\mathbf{L^{11}}$ with a compound of formula HN($\mathbf{R^9}$)-$(CH_2)_{s2}$-$\mathbf{R^8}$, wherein $\mathbf{L^{11}}$ is a displaceable group. This reaction can be performed in the presence of an organic base(such as DIPEA) or an inorganic base (such as potassium carbonate), in a suitable solvent such as DMA or DMF, at a temperature from room temperature to 120°C. Suitable displaceable groups include: a halide, such as chloro, or a methane sulphonate or toluene sulphonate. Compounds can also be prepared by reacting a compound wherein **K'** is -$(CH_2)_{s1}$-N($\mathbf{R^9}$)H with a compound of formula $\mathbf{L^{11}}$-$(CH_2)_{s2}$-$\mathbf{R^8}$, under identical conditions.

(viii.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$-O -$(CH_2)_{s2}$-*
these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-OH with a compound of formula $\mathbf{L^{12}}$-$(CH_2)_{s2}$-$\mathbf{R^8}$, wherein $\mathbf{L^{12}}$ is a displaceable group. This reaction can be performed in the presence of an organic base (such as potassium *t*-butoxide) or an inorganic base (such as sodium hydride), in a suitable solvent such as DMA or DMF, at a temperature from room temperature and 120°C. Suitable displaceable groups include: a halide, such as bromo, or a methane sulphonate or toluene sulphonate. Compounds can also be prepared by reacting a compound wherein **K'** is -$(CH_2)_{s1}$-$\mathbf{L^{12}}$ with a compound of formula HO-$(CH_2)_{s2}$-$\mathbf{R^8}$, under identical conditions.

(ix.) *For compounds of Formula (I) where K is -$(CH_2)_{s1}$-C(O) -$(CH_2)_{s2}$-*
these can be prepared by reacting a compound where **K'** is -$(CH_2)_{s1}$-C(O)-$\mathbf{L^{13}}$ with a Grignard reagent of formula BrMg$(CH_2)_{s2}$-$\mathbf{R^8}$, wherein $\mathbf{L^{13}}$ is a displaceable group. This reaction can be performed in a non-polar solvent such as THF or diethylether at a temperature between room temperature and the boiling point of the solvent. Suitable displaceable groups include: a halide, such as bromo, or a methane sulphonate or toluene sulphonate. Compounds can also be prepared by reacting a

compound wherein **K'** is -$(CH_2)_{s1}$-MgBr with a compound of formula **L**^{13}-C(O)-$(CH_2)_{s2}$-**R**^{8}, under identical conditions.

Process h) reaction of a compound of Formula **XXXVI** with a compound of the formula **L**^{8}-**R**^{5} , can be performed under Friedel Craft conditions, for example in the presence of diethylaluminium chloride in a suitable solvent, such as DCM, in an inert atmosphere such as nitrogen, at a temperature between room temperature and the boiling point of the solvent or under Mannich conditions, for example, formaldehyde and a primary or secondary amine in acetic acid, in an inert atmosphere such as nitrogen at a temperature between room temperature and 100°C.It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of Formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and de-protection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

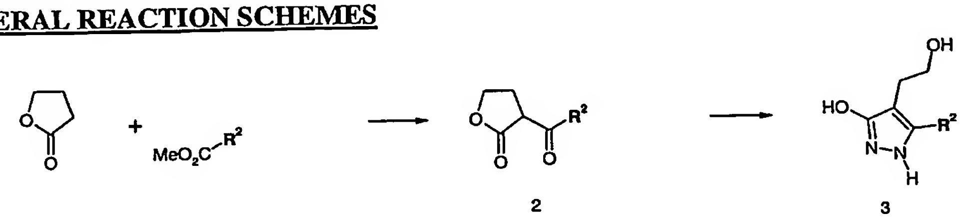
A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The de-protection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The de-protection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

EXPERIMENTAL

GENERAL REACTION SCHEMES

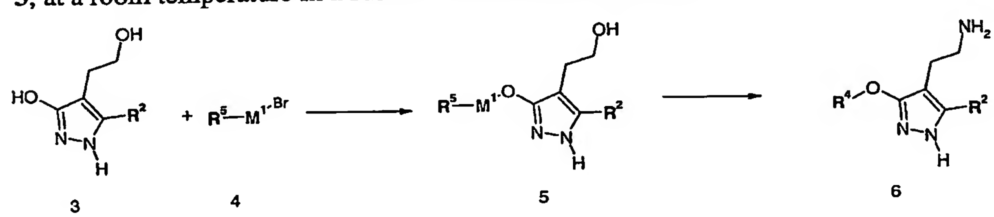


Scheme a

Pyrazoles, such as **3** can be synthesised in two steps (Scheme a):

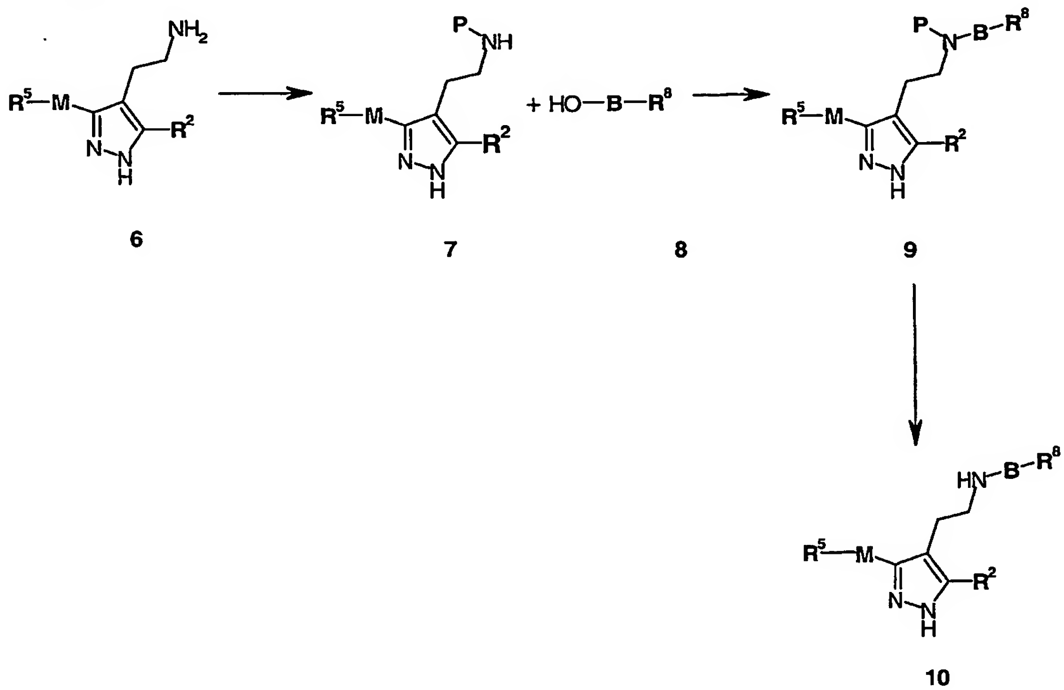
(1) by the reaction of a lactone with the appropriate ester using a Claisen condensation to form a compound of formula **2**, under conditions of an inert atmosphere, such as argon, at a temperature of about 0°C in a suitable solvent such as THF.

(2) followed by cyclization of a compound of formula **2** with hydrazine to form the pyrazole **3**, at a room temperature in a suitable solvent such as ethanol.



Scheme b

The pyrazole **3** can undergo a selective alkylation reaction with a compound of formula **4**, under conditions of an inert atmosphere, such as argon, in the presence of a suitable base, such as potassium carbonate in the a suitable solvent such as DMA at a temperature of about 90°C, to form a compound of formula **5**. Then the amine **6** can be prepared from a compound of formula **5** and phthalimide using a Mitsunobu reaction with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyldiazocarboxylate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof, followec by deprotection with hydrazine to give the (Scheme b).



Scheme c.

A suitable pyrazole **6** can be converted to a compound of formula **10** by incorporation of a suitable protecting group (P)to form a compound of formula **7** , followed by a Mitsunobu reaction with a suitable alcohol **8** to form a compound of formula **9**, followed by deprotection.

EXAMPLES

The invention will now be illustrated with the following non-limiting Examples in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in *vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) chromatography was performed on silica (Merck Keiselgel: Art.9385);

(vii) isolute™ refers to silica (SiO_2) based columns with irregular particles with an average size of 50μm with nominal 60 Å porosity [Source: Jones Chromatography, Ltd., Glamorgan, Wales, United Kingdom].

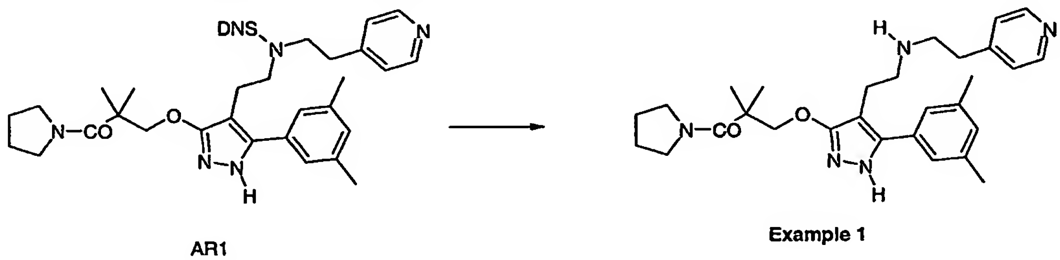
Abbreviations

boc	*t*-butoxycarbonyl
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulphoxide
DMF	dimethylformamide
DNS	2,4-dinitrobenzenesulphonyl
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt	1-hydroxybenzotriazole
LHMDS	lithium bis(trimethylsilyl)amide

THF tetrahydrofuran

Example 1

2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-(2-pyridin-4-ylethyl)ethanamine



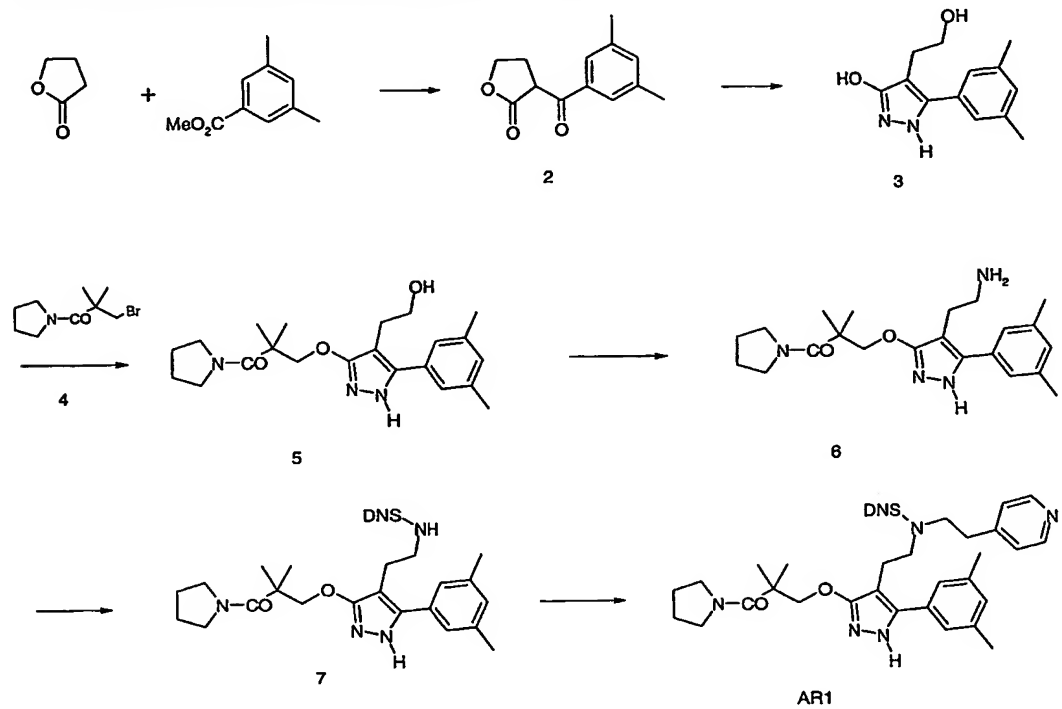
A solution of **AR1** (123 mg ; 0.17 mmol) in CH_2Cl_2 (3 ml) was treated dropwise with propylamine (140 ul ; 1.7 mmol). The mixture was stirred at room temperature for 1h and then purified directly by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (50 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 10% MeOH) to give **Example 1** as a beige solid (83 mg).

Yield : 100%

^{1}H NMR spectrum (DMSO d_6) : 1.27 (s, 6H) ; 1.75 (m, 4H) ; 2.3 (s, 6H) ; 2.55-2.95 (m, 8H) ; 3.5 (m, 4H) ; 4.18 (s, 2H) ; 7.03 (s, 1H) ; 7.10 (s, 2H) ; 7.2 (d, 2H) ; 8.44 (d, 2H), 11.9 (s br, 1H).

MS-ESI : 490 $[M+H]^+$

The starting material AR1 was prepared as follows:-



A solution of methyl 3,5-dimethylbenzoate (25 g ; 152 mmol) and butyrolactone (40 ml ; 520 mmol) in THF (300 ml) under argon was cooled to 0°C and treated dropwise with LHMDS (200 ml ; 200 mmol ; 1M in hexanes). The mixture was stirred and allowed to warm to room temperature overnight. The THF was evaporated. The residue was taken up in Et_2O and the organic phase was washed with sat. aq. $NaHCO_3$, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (20 to 40% EtOAc) to give an oil which slowly crystallised to give 2 as a white solid (9.2 g). During the chromatography, the starting material methyl 3,5-dimethylbenzoate (12.4g) was recovered.

Yield : 55% based on recovered methyl 3,5-dimethylbenzoate.

^{1}H NMR spectrum ($CDCl_3$) : 2.39 (s, 6H) ; 2.5 (m, 1H) ; 2.82 (m, 1H) ; 4.41 (m, 1H) ; 4.51 (m, 2H) ; 7.25 (s, 1H) ; 7.65 (s, 2H).

MS-ESI : 219 $[M+H]^+$

Compound 2 (7.43 g ; 34 mmol) was dissolved in EtOH (200 ml) and hydrazine hydrate (17.2 ml ; 354 mmol) was added. The mixture was stirred for 30 min. The solvent was evaporated and the residue was triturated with pentane to give 3 as a white solid (7.05 g).

Yield : 90%

^{1}H NMR spectrum (DMSO d_6) : 2.32 (s, 6H) ; 2.58 (t, 2H) ; 3.50 (t, 2H) ; 4.8 (br s, 1H) ; 7.01 (s, 1H) ; 7.14 (s, 2H) ; 9.5 (br s, 1H).

MS-ESI : 233 $[M+H]^+$

A mixture of <u>3</u> (4.26 g ; 18.4 mmol) and <u>4</u> (4.51 g ; 19.3 mmol) in DMA (40 ml) under argon was treated with K_2CO_3 (5.07 g ; 36.7 mmol). The mixture was stirred and heated at 90°C for 2h. The mixture was poured into sat. aq. $NaHCO_3$, extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) to give the alcohol <u>5</u> as a pale yellow oil (6.56 g).

Yield : 93%

^{1}H NMR spectrum (DMSO d_6) : 1.30 (s, 6H) ; 1.8 (m, 4H) ; 2.33 (s, 6H) ; 2.55 (m, 2H) ; 3.32 (m, 2H) ; 3.5 (m, 4H) ; 4.17 (s, 2H) ; 4.62 (t, 1H) ; 7.04 (s, 1H) ; 7.16 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 386 $[M+H]^+$

A mixture of <u>5</u> (3.85 g ; 10 mmol), phthalimide (1.62 g ; 11 mmol) and triphenylphosphine (10.5 g ; 40 mmol) in THF (100 ml) at 0°C under argon was treated with DEAD (6.33 ml ; 40 mmol). The mixture was stirred at this temperature for 1h when water was added. The mixture was extracted with Et_2O and the organic phase was washed with water, brine and dried over $MgSO_4$.

Evaporation gave a crude solid which, without further purification, was immediately taken up in EtOH (50 ml) and treated with hydrazine hydrate (5 ml ; 100 mmol). The mixture was stirred for 1.5h and then the EtOH was partially evaporated. Addition of CH_2Cl_2 caused precipitation of phthalhydrazide which was filtered and rinsed with CH_2Cl_2. The filtrate was evaporated and the residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 8% MeOH) to give <u>6</u> as a beige solid (2.34 g).

Yield : 61%

^{1}H NMR spectrum (DMSO d_6) : 1.30 (s, 6H) ; 1.79 (m, 4H) ; 2.33 (s, 6H) ; 2.52 (m, 2H) ; 2.67 (t, 2H) ; 3.5 (m, 4H) ; 4.18 (s, 2H) ; 7.03 (s, 1H) ; 7.14 (s, 2H) ; 8.95 (br s, 1H).

MS-ESI : 385 $[M+H]^+$

A solution of 6 (200 mg ; 0.52 mmol) in CH_2Cl_2 (5 ml) was treated with diisopropylethylamine (135 ul ; 0.78 mmol) and cooled to 0°C. A solution of 2,4-dinitrobenzenesulphonyl chloride (153 mg ; 0.57 mmol) in CH_2Cl_2 (1 ml) was added dropwise and the mixture was allowed to warm to room temperature for 30 min. The mixture was purified directly by flash chromatography eluting with increasingly polar mixtures of $EtOAc/CH_2Cl_2$ (0 to 50% EtOAc) to give 7 as a cream solid (224 mg).

Yield : 70%

^{1}H NMR spectrum (DMSO d_6) : 1.24 (s, 6H) ; 1.75 (m, 4H) ; 2.29 (s, 6H) ; 2.57 (m, 2H) ; 3.11 (m, 2H) ; 3.5 (m, 4H) ; 4.15 (s, 2H) ; 7.0 (s, 1H) ; 7.03 (s, 2H) ; 8.14 (d, 1H) ; 8.56 (q, 1H) ; 8.6 (br s, 1H) ; 8.83 (d, 1H).

MS-ESI : 615 $[M+H]^+$

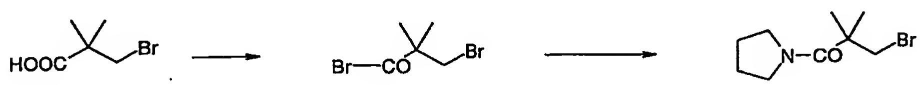
A mixture of 7 (170 mg ; 0.27 mmol), 4-(2-hydroxyethyl)-pyridine (38 mg ; 0.3 mmol) and triphenylphosphine (283 mg ; 1.08 mmol) in THF (10 ml) at 0°C under argon was treated with DEAD (170 ul ; 1.08 mmol). The mixture was allowed to warm to room temperature for 30 min. when water was added. The mixture was extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc) **AR1** as a white solid (123 mg).

Yield : 63%

^{1}H NMR spectrum (DMSO d_6) : 1.27 (s, 6H) ; 1.7 (m, 4H) ; 2.28 (s, 6H) ; 2.69 (t, 2H) ; 2.83 (t, 2H) ; 3.4 (m, 4H) ; 3.48 (t, 2H) ; 3.56 (t, 2H) ; 4.21 (s, 2H) ; 7.01 (s, 1H) ; 7.08 (s, 2H) ; 7.19 (d, 2H) ; 8.15 (d, 1H) ; 8.41 (d, 2H) ; 8.42 (q, 1H) ; 8.89 (d, 1H).

MS-ESI : 720 $[M+H]^+$

Starting material 4 was prepared as follows:-



8 9 4

A mixture of 8 (14.48 g ; 80 mmol) and oxalyl bromide (43.2 g ; 200 mmol) containing one drop of DMF was heated at 50°C for 2h and then cooled. The excess of oxalyl bromide was evaporated and the residue azeotroped with toluene to give crude 9 which was taken up

directly in CH_2Cl_2 (25 ml) and cooled to 0°C. Diisopropylethylamine (14 ml ; 80 mmol) was added followed by a solution of pyrrolidine (3.3 ml ; 40 mmol) in CH_2Cl_2 (30 ml). The mixture was allowed to warm to room temperature overnight and was diluted with CH_2Cl_2, washed with aq. HCl (2N), aq. NaOH (1N), water, brine and dried over MgSO4. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (5 to 10% EtOAc) to give <u>4</u> as a white solid (6.5 g).

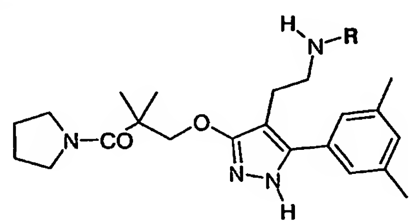
Yield : 70%

^{1}H NMR spectrum (DMSO d_6) : 1.39 (s, 6H) ; 1.9 (m, 4H) ; 3.57 (m, 4H) ; 3.62 (s, 2H)

MS-ESI : 235 $[M+H]^+$

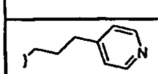
Examples 1.1-1.5

The following examples were prepared in a similar manner to Example 1,



the table shows the **R** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of Example 1 given above:-

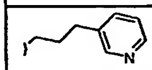
<u>**Example 1.1**</u>

R	AR2 mg ; mmol	CH_2Cl_2 ml	Propylamine μl ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	210 ; 0.28	5	235 ; 2.86	White solid	111 ; 77%	504 $[M+H]^+$

Chromato. – EtOAc and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.27 (s, 6H) ; 1.75 (m, 4H) ; 2.31 (s, 6H) ; 2.57-2.63 (m, 6H) ; 2.75 (m, 2H) ; 3.3-3.7 (m, 4H) ; 4.18 (s, 2H) ; 7.03 (s, 1H) ; 7.11 (s, 2H) ; 7.2 (d, 2H) ; 8.44 (d, 2H); 11.9 (s br, 1H).

Example 1.2

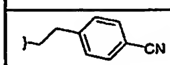
R	AR3 mg ; mmol	CH_2Cl_2 ml	Propylamine μl ; mmol	Prod. Form	Mass mg; Yield	MS-ESI
	120 ; 0.16	3	135 ; 1.63	White solid	60 ; 73%	504 $[M+H]^+$

Chromato. – Ammonia in MeOH(7<u>N</u>)/CH_2Cl_2 (0 to 10% ammonia in MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.27 (s, 6H) ; 1.6-1.9 (m, 6H) ; 2.3 (s, 6H) ; 2.55-2.64 (m, 6H) ; 2.7 (m, 2H) ; 3.3-3.6 (m, 4H) ; 4.17 (s, 2H) ; 7.02 (s, 1H) ; 7.12 (s, 2H) ; 7.29 (dd, 1H) ; 7.58 (d, 1H) ; 8.39 (d, 1H) ; 11.9 (s br, 1H).

Examples 1.3 – 1.5 were prepared by a robot. The last two steps were carried out sequentially without isolation of the intermediates AR4, AR5 or AR6.

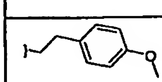
Example 1.3

R	AR4 mg ; mmol	CH_2Cl_2 ml	Ammonia in MeOH(7N) ml	Prod. Form	Mass mg; Yield	MS-ESI
	nd* ; 0.23	5	0.5	oil	18 ; 15%	514 $[M+H]^+$

Chromato. – LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (0 to 100% H_2O)

^{1}H NMR spectrum (DMSO d_6) : 1.26 (s, 6H) ; 1.74 (m, 4H) ; 2.3 (s, 6H) ; 2.55-2.8 (m, 8H) ; 3.4 (m, 4H) ; 4.16 (s, 2H) ; 7.02 (s, 1H) ; 7.10 (s, 2H) ; 7.36 (d, 2H) ; 7.71 (d, 2H) ; 11.9 (s br, 1H).

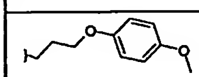
Example 1.4

R	AR5 mg ; mmol	CH_2Cl_2 ml	Ammonia in MeOH(7N) ml	Prod. Form	Mass mg; Yield	MS-ESI
	nd* ; 0.23	5	0.5	oil	15 ; 12%	519 $[M+H]^+$

Chromato. – LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (0 to 100% H_2O)

^{1}H NMR spectrum (DMSO d_6) : 1.27 (s, 6H) ; 1.74 (m, 4H) ; 2.30 (s, 6H) ; 2.5-2.75 (m, 8H) ; 3.5 (m, 4H) ; 3.71 (s, 3H) ; 4.16 (s, 2H) ; 6.81 (d, 2H) ; 7.02 (s, 1H) ; 7.05 (d, 2H) ; 7.11 (s, 2H) ; 11.9 (s br, 1H).

Example 1.5

R	AR6 mg ; mmol	CH_2Cl_2 ml	Ammonia in MeOH(7N) ml	Prod. Form	Mass mg; Yield	MS-ESI
	nd* ; 0.23	5	0.5	oil	23 ; 18%	549 [M+H]$^+$

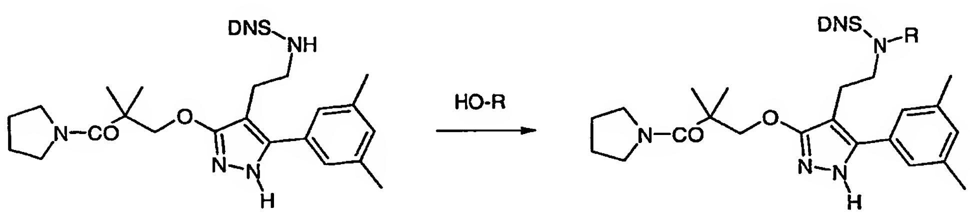
*nd = not determined

Chromato. – LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (0 to 100% H_2O)

^{1}H NMR spectrum (DMSO d_6) : 1.27 (s, 6H) ; 1.77 (m, 4H) ; 2.3 (s, 6H) ; 2.55-2.7 (m, 8H) ; 3.5 (m, 4H) ; 3.68 (s, 3H) ; 3.9 (t, 2H) ; 4.16 (s, 2H) ; 6.81 (m, 4H) ; 7.01 (s, 1H) ; 7.12 (s, 2H) ; 11.9 (s br, 1H).

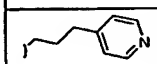
Intermediates for Examples 1-1 - 1.5, AR2 – AR6 respectively

Starting materials **AR2-AR6** were prepared as follows, the table showing the reaction conditions and characteristics for each example, corresponding to the description of **AR1** given above:-



7 AR

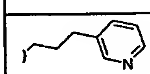
AR2

R	7 mg ; mmol	Alcohol mg ; mmol	PPh3 mg ; mmol	THF ml	DEAD µl ; mmol	Prod. Form	Mass mg ; Yield %	MS-ESI
	200 ; 0.32	55 ; 0.4	340 ; 1.3	10	205 ; 1.3	Yellow solid	216 ; 90%	734 $[M+H]^+$

Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc)

^1H NMR spectrum (DMSO d_6) : 1.22 (s, 6H) ; 1.6-1.8 (m, 4H) ; 1.84 (m, 2H) ; 2.28 (s, 6H) ; 2.55 (m, 2H) ; 2.69 (m, 2H) ; 3.3-3.5 (m, 8H) ; 4.18 (s, 2H) ; 7.00 (s, 1H) ; 7.07 (s, 2H) ; 7.19 (d, 2H) ; 8.17 (d, 1H) ; 8.43 (d, 2H) ; 8.47 (dd, 1H) ; 8.92 (d, 1H) ; 11.9 (s br, 1H).

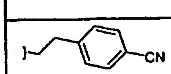
AR3

R	7 mg ; mmol	Alcohol mg ; mmol	PPh3 mg ; mmol	THF ml	DEAD µl ; mmol	Prod. Form	Mass mg ; Yield %	MS-ESI
	200 ; 0.32	55 ; 0.4	340 ; 1.3	5	205 ; 1.3	Yellow solid	122 ; 51%	734 $[M+H]^+$

Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc)

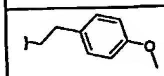
^1H NMR spectrum (DMSO d_6) : 1.22 (s, 6H) ; 1.5-1.9 (m, 4H) ; 1.84 (m, 2H) ; 2.28 (s, 6H) ; 2.55 (m, 2H) ; 2.68 (m, 2H) ; 3.3-3.5 (m, 8H) ; 4.18 (s, 2H) ; 7.00 (s, 1H) ; 7.07 (s, 2H) ; 7.28 (dd, 1H) ; 7.58 (d, 1H) ; 8.17 (d, 1H) ; 8.40 (m, 2H) ; 8.47 (dd, 1H) ; 8.92 (d, 1H) ; 11.9 (s br, 1H).

AR4

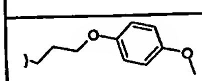
R	7 mg ; mmol	Alcohol mg ; mmol	PPh3 mg ; mmol	THF ml	DTAD mg ; mmol	Prod. Form	Mass mg ; Yield %	MS-ESI
	145 ; 0.23	38 ; 0.26	360 ; 1.38	1	205 ; 0.9	nd*	nd*	nd*

*not determined: Intermediate used directly in last step of robot run without isolation or purification.

AR5

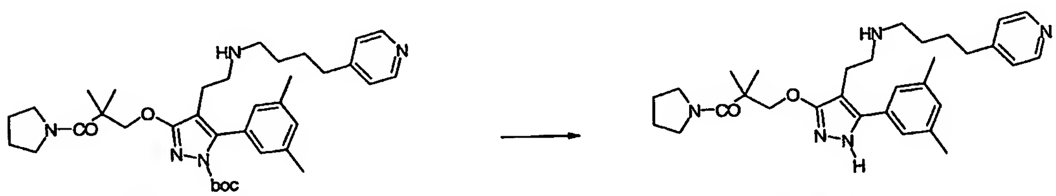
R	7 mg ; mmol	Alcohol mg ; mmol	PPh3 mg ; mmol	THF ml	DTAD mg ; mmol	Prod. Form	Mass mg ; Yield %	MS-ESI
	145 ; 0.23	40 ; 0.26	360 ; 1.38	1	205 ; 0.9	nd*	nd*	nd*

AR6

R	7 mg ; mmol	Alcohol mg ; mmol	PPh3 mg ; mmol	THF ml	DTAD mg ; mmol	Prod. Form	Mass mg ; Yield %	MS-ESI
	145 ; 0.23	47 ; 0.26	360 ; 1.38	1	205 ; 0.9	nd*	nd*	nd*

Example 2

2-[3-(2,2-dimethyl-3-oxo-3-{pyrrolidin-1-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-(4-pyridin-4-ylbutyl)ethanamine



Ab6 Example 2

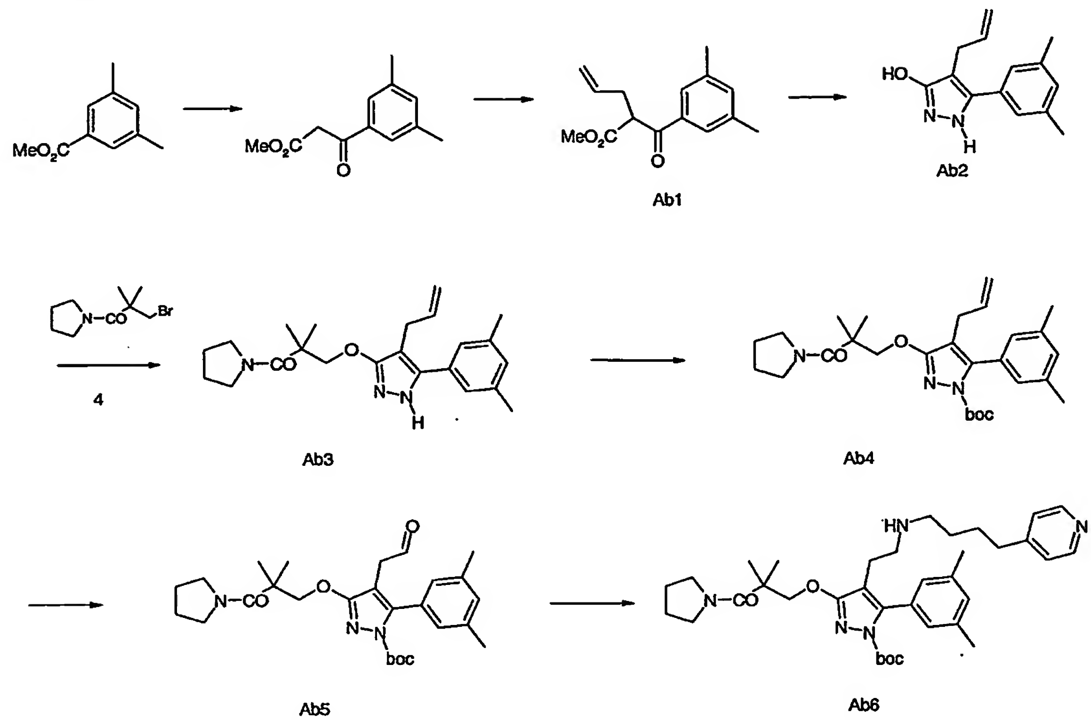
Dry, gaseous HCl was bubbled through a solution of **Ab6** (180 mg ; 0.29 mmol) in CH_2Cl_2 (30 ml) until no Ab6 remained. The mixture was treated with iced sat. aq. $NaHCO_3$, extracted with CH_2Cl_2 and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ammonia in MeOH(7N)/CH_2Cl_2 (0 to 10% ammonia in MeOH) to give **Example 2** (114 mg).

Yield : 76%

^{1}H NMR spectrum ($CDCl_3$) : 1.38 (s, 6H) ; 1.45 (m, 2H) ; 1.6 (m, 2H) ; 1.84 (m, 4H) ; 2.33 (s, 6H) ; 2.59 (m, 4H) ; 2.65 (t, 2H) ; 2.77 (t, 2H) ; 3.57 ; (m, 4H) ; 4.32 (s, 2H) ; 7.01 (s, 1H) ; 7.04 (s, 2H) ; 7.08 (d, 2H) ; 8.47 (d, 2H) ; 11.9 (s br, 1H).

MS-ESI : 518 $[M+H]^+$

The starting material **Ab6** was prepared as follows:-



A solution of methyl 3,5-dimethylbenzoate (50 g ; 300 mmol) in DME (80 ml) was added to a suspension of NaH (26.8 g ; 60% in oil ; 670 mmol) in DME (80 ml) under argon. The mixture was heated to reflux and a solution of methyl acetate (45 g ; 610 mmol) in DME (40 ml) added dropwise. The mixture was heated for a further 4 h under reflux. The mixture was cooled and the excess of NaH destroyed by the dropwise addition of MeOH (40 ml). The mixture was poured into dilute HCl (2N), extracted with Et_2O and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with Et_2O /hexanes (10% Et_2O) to give methyl 4-(3',5'-dimethylphenyl) acetoacetate as a yellow oil (31 g).

Yield : 50%

^{1}H NMR spectrum ($CDCl_3$) : This compound exists as a 4/1 mixture of keto (k) and enol (e) forms : 2.36 (s, 6H)(e) ; 2.38 (s, 6H)(k) ; 3.76 (s, 3H)(k) ; 3.81 (s, 3H)(e) ; 4.03 (s, 2H)(k) ; 5.65 (s, 1H)(e) ; 7.11 (s, 1H)(e) ; 7.27 (s, 1H)(k) ; 7.4 (s, 2H)(e) ; 7.56 (s, 2H)(k) ; 12.48 (s, 1H)(e).

MS-ESI : 207 $[M+H]^+$

NaH (2.44 g ; 60% in oil ; 61 mmol) was added in small portions to a solution of methyl 4-(3',5'-dimethylphenyl) acetoacetate (9.66 g ; 46.9 mmol) in DMF (50 ml) at 0°C under argon. The mixture was stirred and allowed to warm to room temperature for 30 min. A solution of allyl bromide (4.05 ml ; 46.9 mmol) in DMF (5 ml) was added dropwise and the mixture stirred for a further 2 h. The mixture was poured into H_2O, extracted with Et_2O and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with Et_2O /hexanes (0 to 15% Et_2O) to give **Ab1** as a pale yellow oil (8.3 g).

Yield : 72%

^{1}H NMR spectrum ($CDCl_3$) : 2.39 (s, 6H) ; 2.76 (m, 2H) ; 3.70 (s, 3H) ; 4.43 (t, 1H) ; 5.08 (m, 1H) ; 5.15 (m, 1H) ; 5.82 (m, 1H) ; 7.24 (s, 1H) ; 7.60 (s, 2H).

MS-ESI : 247 $[M+H]^+$

A solution of **Ab1** (3.4 g ; 13 mmol) in EtOH (30 ml) was treated with hydrazine hydrate (3.9 ml ; 78 mmol) and heated under reflux for 3 h. The EtOH was evaporated and the residue triturated with Et_2O. The precipitate was filtered, washed with H_2O and dried to give **Ab2** as a white powder (2.8 g).

Yield : 95%

^{1}H NMR spectrum ($CDCl_3$ + TFAD) : 2.42 (s, 6H) ; 3.32 (d, 2H) ; 5.11 (d, 1H) ; 5.19 (d, 1H); 5.97 (m, 1H) ; 7.16 (s, 2H) ; 7.24 (s, 1H) ; 10.95 (s br 1H).

MS-ESI : 229 $[M+H]^+$

A mixture of **Ab2** (2.1 g ; 9.2 mmol) and **4** (2.15 g ; 9.2 mmol) in DMA (30 ml) under argon was treated with K_2CO_3 (2.54 g ; 18.4 mmol). The mixture was stirred and heated at 80°C for 2h. The mixture was poured into sat. aq. $NaHCO_3$, extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (50 to 100% EtOAc) to give **Ab3** as a pale yellow solid (2.8 g).

Yield : 80%

^{1}H NMR spectrum ($CDCl_3$) : 1.35 (s, 6H) ; 1.8 (m, 4H) ; 2.32 (s, 6H) ; 3.14 (m, 2H) ; 3.55 (m, 4H) ; 4.18 (s, 2H) ; 4.97 (m, 2H) ; 5.89 (m, 1H) ; 7.02 (s, 1H) ; 7.03 (s, 2H) ; 8.9 (br s, 1H).
MS-ESI : 382 $[M+H]^+$

A mixture of **Ab3** (2.59 g ; 6.8 mmol) and $(BOC)_2O$ (7.4 g ; 34 mmol) in CH_3CN (80 ml) was treated with Et_3N (1.9 ml ; 13.6 mmol). The mixture was heated at 80°C for 3h. The solvent was evaporated, the mixture was poured into sat. aq. $NaHCO_3$, extracted with Et_2O and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 25% EtOAc) to give **Ab4** as a white solid (2.51 g).
Yield : 76%
^{1}H NMR spectrum ($CDCl_3$) : 1.18 (s, 9H) ; 1.34 (s, 6H) ; 1.8 (m, 4H) ; 2.3 (s, 6H) ; 2.85 (m, 2H) ; 3.54 (m, 4H) ; 4.43 (s, 2H) ; 4.87 (m, 2H) ; 5.73 (m, 1H) ; 6.8 (s, 2H) ; 6.98 (s, 1H).
MS-ESI : 482 $[M+H]^+$

4-Methyl-morpholoine-N-oxide (1.6 ml ; 60% solution in H_2O) was added to a solution of **Ab4** (2.21 g ; 4.6 mmol) in THF (100 ml) and H_2O (30 ml). The mixture was cooled to 0°C and a solution of OsO_4 (92 mg ; 0.36 mmol) in *t*-BuOH (1.8 ml) was added dropwise. The mixture was allowed to warm to room temperature for 6 h. The reaction was quenched by the addition of aq. $Na_2S_2O_5$ (1.75g) in H_2O (50 ml). The THF was evaporated and the mixture extracted with EtOAc. The organic phase was washed with water, brine and dried over $MgSO_4$. The residue (2.21 g) was taken up in THF (100 ml) and H_2O (30 ml) and treated with $NaIO_4$. The mixture was stirred overnight. The THF was evaporated and the mixture extracted with EtOAc. The organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 50% EtOAc) to give **Ab5** as a buff solid (1.63 g).
Yield : 73%

^{1}H NMR spectrum ($CDCl_3$) : 1.21 (s, 9H) ; 1.34 (s, 6H) ; 1.9 (m, 4H) ; 2.32 (s, 6H) ; 3.23 (d, 2H) ; 3.55 (m, 4H) ; 4.47 (s, 2H) ; 6.8 (s, 2H) ; 7.01 (s, 1H) ; 9.56 (d, 1H).
MS-ESI : 484 $[M+H]^+$

A solution of **Ab5** (360 mg ; 0.74 mmol) and 4-(4-aminobutyl)-pyridine (123 mg ; 0.82 mmol) in MeOH (6 ml) was treated with $NaBH_3CN$ (52 mg ; 0.82 mmol). The mixture was

cooled to 0°C and acetic acid (45 μl ; 0.82 mmol) was added. The mixture was allowed to warm to room temperature for 2 h and evaporated. The residue was treated with aq. K_2CO_3 (10%) and the mixture extracted with EtOAc. The organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with EtOAc and then increasingly polar mixtures of $MeOH/CH_2Cl_2$ (0 to 5% MeOH) to give **Ab6** as an oil (180 mg).

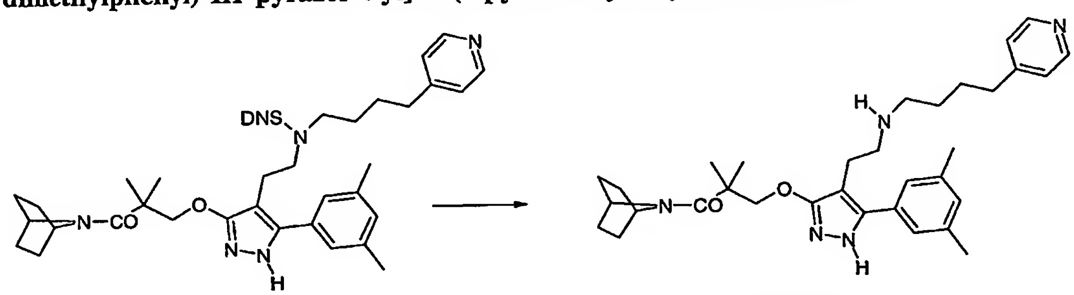
Yield : 40%

^{1}H NMR spectrum ($CDCl_3$) : 1.20 (s, 9H) ; 1.37 (s, 6H) ; 1.61 (m, 2H) ; 1.87 (m, 6H) ; 2.31 (s, 6H) ; 2.48 (m, 2H) ; 2.62 (m, 4H) ; 2.76 (m, 2H) ; 3.57 (m, 4H) ; 4.45 (s, 2H) ; 6.8 (s, 2H) ; 7.0 (s, 1H) ; 7.08 (d, 2H) ; 8.47 (d, 2H).

MS-ESI : 618 $[M+H]^+$

Example 3

2-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-(4-pyridin-4-ylbutyl)-ethanamine



BR1 Example 3

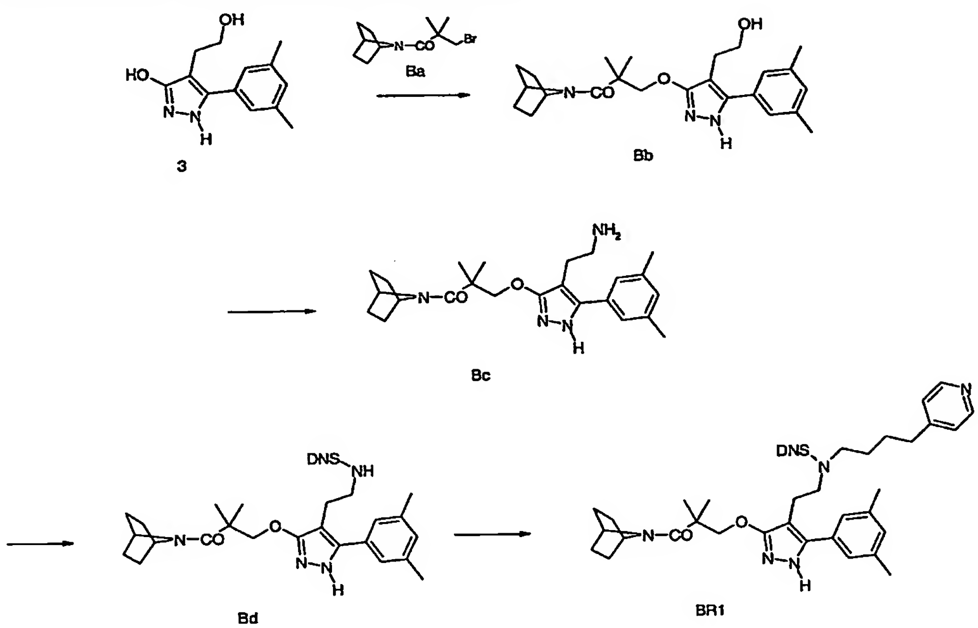
A solution of **BR1** (322 mg ; 0.41 mmol) in CH_2Cl_2 (5 ml) was treated dropwise with propylamine (340 μl ; 4.1 mmol). The mixture was stirred at room temperature for 1h and then purified directly by flash chromatography eluting with increasingly polar mixtures of $MeOH/CH_2Cl_2$ (0 to 10% MeOH) to give **Example 3** as a white solid (219 mg).

Yield : 98 %

^{1}H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.43 (m, 6H) ; 1.61 (m, 6H) ; 2.3 (s, 6H) ; 2.59 (m, 4H) ; 2.65 (m, 2H) ; 2.75 (m, 2H) ; 4.16 (s, 2H) ; 4.57 (s, 2H) ; 7.02 (s, 1H) ; 7.11 (s, 2H) ; 7.21 (d, 2H) ; 8.44 (m, 2H) ; 11.8 (s br 1H).

MS-ESI : 544 $[M+H]^+$

Starting material **BR1** was prepared as follows:-



A mixture of **3** (4.64 g ; 20 mmol) and **Ba** (5.72 g ; 22 mmol) in DMA (50 ml) under argon was treated with K_2CO_3 (5.52 g ; 40 mmol). The mixture was stirred and heated at 70°C for 6h. The mixture was poured into sat. aq. $NaHCO_3$, extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 50% EtOAc) to give the alcohol **Bb** as a pale yellow oil (7.58 g).

Yield : 92%

^{1}H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 2.31 (s, 6H) ; 2.53 (m, 2H) ; 3.46 (m, 2H) ; 4.14 (s, 2H) ; 4.58 (s, 2H) ; 4.61 (t, 1H) ; 7.02 (s, 1H) ; 7.14 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 412 $[M+H]^+$

A mixture of **Bb** (3.29 g ; 8 mmol), phthalimide (2.35 g ; 16 mmol) and triphenylphosphine (12.5 g ; 48 mmol) in THF (50 ml) was cooled to –20°C under argon and treated dropwise with DEAD (7.6 ml ; 48 mmol). The mixture was allowed to warm to 10°C for 1h when water was added and the THF evaporated. The mixture was extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$.

Evaporation gave a crude solid which, without further purification, was immediately taken up in EtOH (200 ml) and treated with hydrazine hydrate (16 ml ; 320 mmol). The mixture was stirred for 2h and then the EtOH was partially evaporated. Addition of CH_2Cl_2 caused precipitation of phthalhydrazide which was filtered and rinsed with CH_2Cl_2. The filtrate was evaporated and the residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH) to give **Bc** as a pale beige solid (2.53 g).

Yield : 77%

^{1}H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 2.31 (s, 6H) ; 2.46 (m, 2H) ; 2.65 (t, 2H) ; 4.15 (s, 2H) ; 4.58 (m, 2H) ; 7.01 (s, 1H) ; 7.12 (s, 2H) ; 11.8 (s br 1H).

MS-ESI : 411 $[M+H]^+$

A solution of **Bc** (1.43 g ; 3.48 mmol) in CH_2Cl_2 (30 ml) was treated with diisopropylethylamine (910 μl ; 5.22 mmol) and cooled to 0°C. A solution of 2,4-dinitrobenzenesulphonyl chloride (1.02 g ; 3.84 mmol) in CH_2Cl_2 (10 ml) was added dropwise and the mixture was allowed to warm to room temperature for 30 min. The mixture was poured into sat. aq. $NaHCO_3$, extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of $EtOAc/CH_2Cl_2$ (0 to 20% EtOAc) to give **Bd** as a cream solid (1.1 g).

Yield : 50%

^{1}H NMR spectrum (DMSO d_6) : 1.22 (s, 6H) ; 1.41 (m, 4H) ; 1.59 (s, 4H) ; 2. 3 (s, 6H) ; 2.57 (m, 2H) ; 3.11 (m, 2H) ; 4.12 (s, 2H) ; 4.55 (s, 2H) ; 7.0 (s, 1H) ; 7.03 (s, 2H) ; 8.17 (d, 1H) ; 8.59 (m, 2H) ; 8.83 (d, 1H) ; 11.8 (s br 1H).

MS-ESI : 641 $[M+H]^+$

A mixture of **Bd** (300 mg ; 0.43 mmol), 4-(4-hydroxybutyl)-pyridine (84 mg ; 0.56 mmol) and triphenylphosphine (495 mg ; 1.87 mmol) in THF (10 ml) at 0°C under argon was treated dropwise with DEAD (300 μl ; 1.87 mmol). The mixture was allowed to warm to room temperature for 30 min. when water was added. The THF was evaporated, the mixture extracted with EtOAc and the organic phase washed with water, brine and dried over $MgSO_4$.

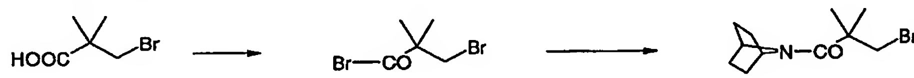
The residue was purified by flash chromatography eluting with increasingly polar mixtures of $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc) **BR1** as a white solid (322 mg).

Yield : 89%

^{1}H NMR spectrum (DMSO d_6) : 1.24 (s, 6H) ; 1.38 (m, 4H) ; 1.54 (m, 8H) ; 2.29 (s, 6H) ; 2.57 (m, 2H) ; 2.64 (m, 2H) ; 3.36 (m, 4H) ; 4.18 (s, 2H) ; 4.52 (m, 2H) ; 7.02 (s, 1H) ; 7.08 (s, 2H) ; 7.16 (d, 2H) ; 8.20 (d, 1H) ; 8.41 (d, 2H) ; 8.47 (dd, 1H) ; 8.91 (d, 1H) ; 11.8 (s br 1H).

MS-ESI : 774 $[M+H]^+$

Starting material **Ba** was prepared as follows:-



8 9 Ba

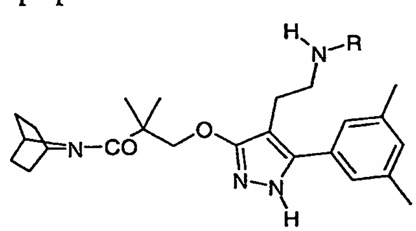
A mixture of **8** (14.48 g ; 80 mmol) and oxalyl bromide (43.2 g ; 200 mmol) containing one drop of DMF was heated at 50°C for 2h and then cooled. The excess of oxalyl bromide was evaporated and the residue azeotroped with toluene to give crude **9** which was taken up in CH_2Cl_2 (25 ml) and cooled to 0°C. Diisopropylethylamine (14 ml ; 80 mmol) was added followed by 2.2.1-azabicycloheptane hydrochloride (5.34 g ; 40 mmol). The mixture was allowed to warm to room temperature overnight and was diluted with CH_2Cl_2, washed with aq. HCl (2N), aq. NaOH (1N), water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with CH_2Cl_2 to give **Ba** as a white solid (7.4 g).

Yield : 71%

^{1}H NMR spectrum ($CDCl_3$) : 1.36 (s, 6H) ; 1.49 (m, 4H) ; 1.82 (m, 4H) ; 3.59 (s, 2H) ; 4.61 (s, 2H).

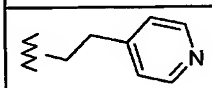
Examples 3.1-3.5

The following examples were prepared in a similar manner to Example 3,



the table shows the **R** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of Example 3 given above:-

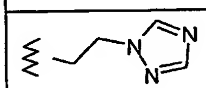
Example 3.1

R	BR2 mg ; mmol	CH_2Cl_2 ml	Propylamine µl ; mmol	Mass mg ; Yield	MS-ESI
	292 ; 0.39	5	320 ; 3.9	161 ; 80%	516 [M+H]+

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.6 (m, 4H) ; 2.29 (s, 6H) ; 2.55 (m, 2H) ; 2.71 (m, 4H) ; 2.81 (m, 2H) ; 4.15 (s, 2H) ; 4.56 (s, 2H) ; 7.02 (s, 1H) ; 7.10 (s, 2H) ; 7.2 (d, 2H) ; 8.43 (dd, 2H) ; 11.7 (s br 1H).

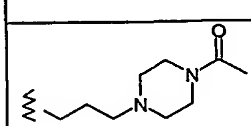
Example 3.2

R	BR3 mg ; mmol	CH_2Cl_2 ml	Propylamine µl ; mmol	Mass mg ; Yield	MS-ESI
	123 ; 0.17	3	140 ; 1.67	58 ; 68%	506 [M+H]+

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.3 (s, 6H) ; 2.46 (m, 2H) ; 2.64 (m, 2H) ; 2.88 (m, 2H) ; 4.15 (s, 2H) ; 4.19 (t, 2H) ; 4.57 (s, 2H) ; 7.01 (s, 1H) ; 7.09 (s, 2H) ; 7.92 (s, 1H) ; 8.42 (s, 1H) ; 11.9 (s br, 1H).

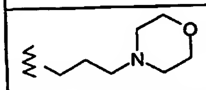
Example 3.3

R	BR4 mg ; mmol	CH_2Cl_2 ml	Propylamine µl ; mmol	Mass mg ; Yield	MS-ESI
	96 ; 0.12	3	140 ; 1.67	50 ; 72%	579 [M+H]+

Chromato. – EtOAc and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.26 (s, 6H) ; 1.44 (m, 4H) ; 1.61 (m, 6H) ; 1.97 (s, 3H) 2.25 (s, 2H) ; 2.32 (s, 6H) ; 2.4-2.85 (m, 14H) ; 4.16 (s, 2H) ; 4.58 (s, 2H) ; 7.04 (s, 1H) ; 7.11 (s, 2H) ; 11.8 (s, 1H).

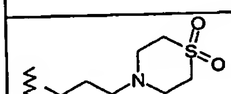
Example 3.4

R	BR5 mg ; mmol	CH_2Cl_2 ml	Propylamine μl ; mmol	Mass mg ; Yield	MS-ESI
	167 ; 0.22	3	180 ; 2.2	30 ; 25%	538 [M+H]$^+$

Chromato. – EtOAc and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.26 (s, 6H) ; 1.44 (m, 4H) ; 1.57 (m, 2H) ; 1.62 (m, 4H) ; 2.27 (m, 6H) ; 2.32 (s, 6H) ; 2.5-2.85 (m, 6H) ; 3.52 (s, 4H) ; 4.16 (s, 2H) ; 4.58 (s, 2H) ; 7.03 (s, 1H) ; 7.12 (s, 2H) ; 11.8 (s, 1H).

Example 3.5

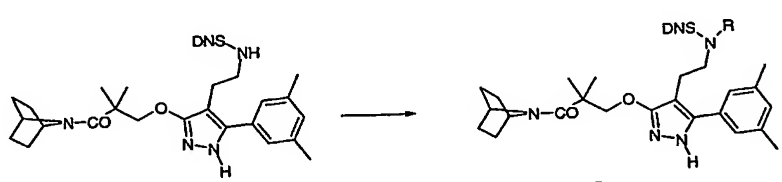
R	BR6 mg ; mmol	CH_2Cl_2 ml	Propylamine μl ; mmol	Mass mg ; Yield	MS-ESI
	194 ; 0.24	3	195 ; 2.4	93 ; 66%	586 [M+H]$^+$

Chromato. – EtOAc and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.26 (s, 6H) ; 1.44 (m, 4H) ; 1.55 (m, 2H) ; 1.61 (m, 4H) ; 2.32 (s, 6H) ; 2.4-2.85 (m, 8H) ; 2.82 (s, 4H) ; 3.04 (m, 4H) ; 4.16 (s, 2H) ; 4.58 (s, 2H) ; 7.03 (s, 1H) ; 7.12 (s, 2H) ; 11.8 (s, 1H).

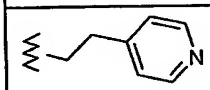
Intermediates for Examples 3.1-3.5, BR2 – BR6 respectively

Starting materials **BR2-6** were prepared as follows, the table showing the reaction conditions and characteristics for each example, corresponding to the description of **Example 3** given above:-



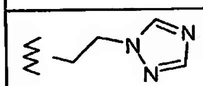
Bd BR

BR2

R	**Bd** mg ; mmol	Alcohol mg ; mmol	PPh_3 mg ; mmol	THF ml	DEAD μl ; mmol	Mass mg ; Yield	MS-ESI
	300 ; 0.47	70 ; 0.56	495 ; 1.87	10	290 ; 1.84	292 ; 83%	746 $[M+H]^+$

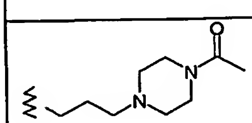
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc)

BR3

R	**Bd** mg ; mmol	Alcohol mg ; mmol	PPh_3 mg ; mmol	THF ml	DEAD μl ; mmol	Mass mg ; Yield	MS-ESI
	150 ; 0.23	32 ; 0.28	362 ; 1.38	5	145 ; 0.92	123 ; 72%	736 $[M+H]^+$

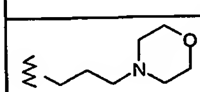
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc)

BR4

R	**Bd** mg ; mmol	Alcohol mg ; mmol	PPh_3 mg ; mmol	THF ml	DEAD μl ; mmol	Mass mg ; Yield	MS-ESI
	150 ; 0.23	53 ; 0.28	362 ; 1.38	5	200 ; 1.26	96 ; 51%	809 $[M+H]^+$

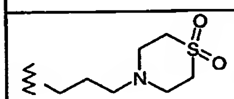
Chromato. – $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc) and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

BR5

R	**Bd** mg ; mmol	Alcohol mg ; mmol	PPh_3 mg ; mmol	THF ml	DEAD μl ; mmol	Mass mg ; Yield %	MS-ESI
	200 ; 0.31	54 ; 0.37	490 ; 1.86	5	270 ; 1.72	167 ; 70%	768 $[M+H]^+$

Chromato. – EtOAc and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

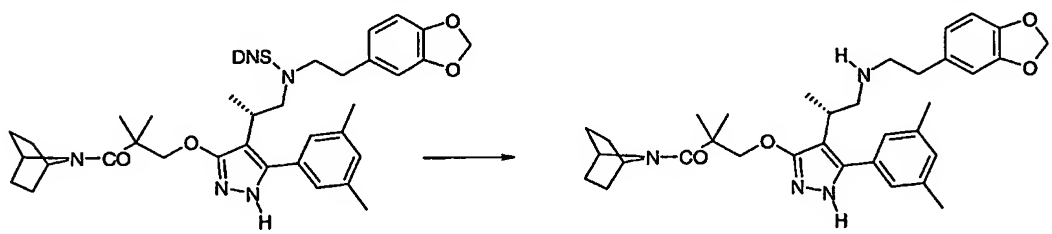
<u>BR6</u>

R	<u>Bd</u> mg ; mmol	Alcohol mg ; mmol	PPh_3 mg ; mmol	THF ml	DEAD μl ; mmol	Mass mg ; Yield %	MS-ESI
	200 ; 0.31	72 ; 0.37	490 ; 1.86	5	270 ; 1.72	194 ; 77%	816 $[M+H]^+$

Chromato. – EtOAc and then MeOH/CH_2Cl_2 (0 to 10% MeOH).

<u>Example 4</u>

2-[3-(2,2-dimethyl-3-oxo-3-azabicyclo[2.2.1]heptan-7-ylpropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine



CR17 Example 4

A solution of partially purified* <u>Cg17</u> (4.2 g ; from 2.3 mmol of <u>Cf</u>) in CH_2Cl_2 (30 ml) under nitrogen was treated dropwise with n-propylamine (1.36 ml ; 23 mmol) at room temperature. The mixture was stirred at room temperature for 2h, the solvents evaporated and the residue purified directly by flash chromatography eluting with increasingly polar mixtures of EtOAc and then MeOH/CH_2Cl_2 (0 to 15% MeOH) to give **Example 4** as a beige solid (768 mg).

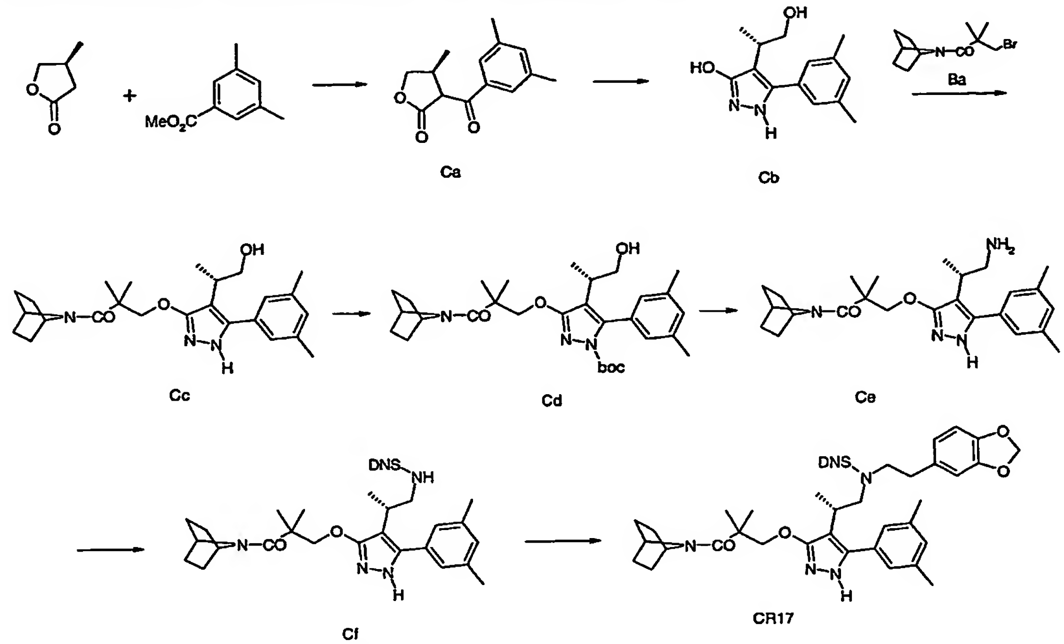
*Contains some Ph_3PO

Yield : 59% for last two steps.

^1H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.60 (m, 4H) ; 2.3 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 5.94 (s, 2H) ; 6.55 (d, 1H) ; 6.69 (s, 1H) ; 6.76 (d, 1H) ; 7.03 (s, 1H) ; 7.04 (s, 2H) ; 11.8 (s br 1H).

MS-ESI : 573 $[M+H]^+$

Starting materials Ce, Cf and CR17 were prepared as follows:-



A solution of methyl 3,5-dimethylbenzoate (148 g ; 0.9 mol) and 3S-methylbutyrolactone (90 g ; 0.9 mol) in THF (2.4 l) under argon was cooled to 0°C and treated dropwise rapidly with LHMDS (1.35 l ; 1.35 mol ; 1M in hexanes). The mixture was stirred for 2h while the temperature was maintained below 10°C. The mixture was poured into dilute HCl (2N, 800ml) at 0°C. Further dilute HCl (2N) was added until the pH reached 1.6. The THF was evaporated and the residual aqueous phase was extracted with EtOAc. The organic phase was washed with sat. aq. $NaHCO_3$, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (10 to 15% EtOAc) to give Ca as a colourless oil (127.7 g).

Yield : 61%.

^{1}H NMR spectrum (DMSO d_6) : 1.09 (td, 3H) ; 2.36 (s, 6H) ; 3.05 (m, 1H) ; 3.93 (t, 1H) ; 4.50 (t, 1H) ; 4.78 (d, 1H) ; 7.36 (s, 1H) ; 7.67 (s, 2H).

MS-ESI : 233 [M+H]$^+$

Compound Ca (127.5 g ; 0.55 mol) was dissolved in EtOH (2.0 l) and hydrazine hydrate (27 ml ; 0.55 mol) was added. The mixture was stirred overnight at room temperature. Dilute HCl (12N ; 12 ml) was added and the mixture stirred for a further 1h. The precipitate was filtered

to give **Cb** as a white solid (63 g). Crystallisation from the mother liquors yielded further batches of **Cb** (29 g).

Yield : 68%

^{1}H NMR spectrum (DMSO d_6) : 1.15 (d, 3H) ; 2.23 (s, 6H) ; 2.77 (m, 1H) ; 3.53 (d, 2H) ; 4.77 (br s, 1H) ; 7.01 (s, 1H) ; 7.04 (s, 2H) ; 9.5 (br s, 1H).

MS-ESI : 247 $[M+H]^+$

A mixture of **Cb** (50 g ; 0.20 mol) and **Ba** (60 g ; 0.23 mol) in DMA (350 ml) under argon was treated with K_2CO_3 (56 g ; 0.41 mol). The mixture was stirred and heated at 80°C overnight. The mixture was cooled and poured into a stirred mixture of sat. aq. $NaHCO_3/H_2O$ (1:2.5). The precipitate was filtered, washed abundantly with water and dried, to give the alcohol **Cc** as a pale beige solid. (84.5 g).

Yield : 99%

^{1}H NMR spectrum (DMSO d_6) : 1.12 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 2.31 (s, 6H) ; 2.75 (m, 1H) ; 3.46 (m, 2H) ; 4.14 (m, 2H) ; 4.51 (br s, 1H) ; 4.58 (m, 2H) ; 7.03 (s, 1H) ; 7.06 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 426 $[M+H]^+$

A solution of **Cc** (42 g ; 0.1 mol) in CH_2Cl_2 (800 ml) under argon was treated with acetonitrile (3 l) and DMAP (250 mg ; cat.). The mixture was stirred and cooled to 0°C and a solution of BOCOBOC (24 g ; 0.11 mol) in acetonitrile (100 ML) was added slowly, dropwise. The mixture was allowed to warm to room temperature until no **Cc** remained (~1 day) and was poured into water (2 l) and stirred for 4 h. The organic solvents were evaporated. The mixture was extracted with CH_2Cl_2 and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/ CH_2Cl_2 (20 to 50% EtOAc) to give **Cd** as a colourless foam (25.5 g).

Yield : 50%

^{1}H NMR spectrum (DMSO d_6) : 1.02 (d, 3H) ; 1.16 (s, 9H) ; 1.270 (s, 6H) ; 1.44 (m, 4H) ; 1.62 (m, 4H) ; 2.29 (s, 6H) ; 2.33 (m, 1H) ; 3.38 (m, 2H) ; 4.23 (m, 2H) ; 4.54 (m, 1H) ; 4.59 (s, 2H) ; 6.89 (s, 1H) ; 7.05 (s, 2H).

MS-ESI : 526 $[M+H]^+$

A solution of **Cd** (50.9 g ; 97 mmol), phthalimide (17 g ; 116 mmol) and triphenyl phosphine (38 g ; 145 mmol) in THF (1 l) under argon was cooled to 0°C and treated rapidly, portionwise with DTAD (33.3 g ; 145 mmol). The mixture was allowed to warm to room temperature for 2 h 30 min. Water (500 ml) was added to the mixture and the organic solvent evaporated. The mixture was extracted with CH_2Cl_2 and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 15% EtOAc) to give a cream foam (48.4 g) which was dissolved in EtOH (1.5 l). The mixture was treated with hydrazine hydrate (143 ml ; 2.95 mol) at room temperature and was stirred for a further 26 h. The precipitate was filtered and the residue purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (5 to 15% MeOH) to give **Ce** as a white solid (31.4 g).

Yield : 77%

^{1}H NMR spectrum (DMSO d_6) : 1.12 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.31 (s, 6H) ; 2.63 (m, 2H) ; 2.72 (m, 1H) ; 4.15 (m, 2H) ; 4.57 (m, 2H) ; 7.02 (s, 1H) ; 7.06 (s, 2H) ; 8.9 (br s, 1H).

MS-ESI : 425 $[M+H]^+$

A solution of **Ce** (1.5g ; 3.58 mmol) in THF (70 ml) was cooled to 0°C under argon. DIEA (810 μl ; 4.65 mmol) was added followed by a solution of DNOSCl (1.04 g ; 3.9 mmol) in THF (20 ml). The mixture was allowed to warm to room temperature for 2 h and was treated with aq. HCl (1N). The mixture was extracted with CH_2Cl_2 and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) to give **Cf** as a cream foam (2.07 g).

Yield : 88%

^{1}H NMR spectrum (DMSO d_6) : 1.10 (d, 3H) ; 1.23 (s, 6H) ; 1.41 (m, 4H) ; 1.58 (m, 4H) ; 2.29 (s, 6H) ; 2.83 (m, 1H) ; 3.19 (m, 2H) ; 4.13 (m, 2H) ; 4.55 (m, 2H) ; 6.95 (s, 2H) ; 6.98 (s, 1H) ; 8.12 (d, 1H) ; 8.49 (br s, 1H) ; 8.52 (q, 1H) ; 8.79 (d, 1H).

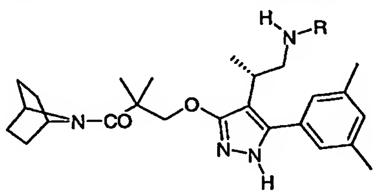
MS-ESI : 655 $[M+H]^+$

A mixture of **Cf** (1.5 g ; 2.3 mmol), the corresponding alcohol (575 mg ; 3.45 mmol) and triphenylphosphine (3.67 g ; 14 mmol) in THF (50 ml) at 0°C under argon was treated with DTAD (2.12 g ; 9.2 mmol). The mixture was allowed to warm to room temperature for 1 h

when water was added. The mixture was extracted with CH_2Cl_2 and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (0 to 50%) and then EtOAc/CH_2Cl_2 (0 to 100% EtOAc) to give **CR17** as a beige solid (4.2 g). This partially purified intermediate (containing some Ph_3PO) was used directly in the final step.

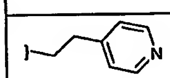
Example 4.1-4.54

The following examples were prepared using the same methodology as Example 4,



The table shows the **R** group relating to the above structure, the reaction conditions and characteristics of each example, corresponding to the description of the preparation of Example 4 given above: -

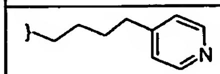
Example 4.1

R	CR1 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	100 ; 0.13	5	0.11 ; 1.3	53 ; 78%	530 $[M+H]^+$

Chromato. – EtOAc and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.12 (d, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.60 (m, 4H) ; 2.28 (s, 6H) ; 2.6-2.9 (m, 7H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 7.03 (s, 3H) ; 7.12 (d, 2H) ; 8.39 (d, 2H) ; 11.8 (s br 1H).

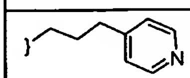
Example 4.2

R	CR2 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	202 ; 0.25	3	0.21 ; 2.5	130 ; 91%	558 $[M+H]^+$

Chromato. - EtOAc and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.35 (m, 2H) ; 1.42 (m, 4H) ; 1.53 (m, 2H) ; 1.61 (m, 4H) ; 2.29 (s, 6H) ; 2.5-2.95 (m, 7H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 7.03 (s, 1H) ; 7.05 (s, 2H) ; 7.17 (d, 2H) ; 8.42 (d, 2H) 11.8 (s br 1H).

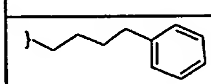
Example 4.3

R	CR3 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	68 ; 0.09	3	0.08 ; 0.88	42 ; 87%	544 $[M+H]^+$

Chromato. - EtOAc and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6 – TFAd) : 1.25 (m, 9H) ; 1.43 (m, 4H) ; 1.60 (m, 4H) ; 1.97 (m, 2H) ; 2.32 (s, 6H) ; 2.8-3.15 (m, 7H) ; 4.20 (s, 2H) ; 4.55 (s, 2H) ; 7.03 (s, 2H) ; 7.07 (s, 1H) 7.96 (d, 2H) ; 8.89 (d, 2H) ; 11.8 (s br 1H).

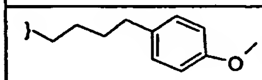
Example 4.4

R	CR4 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	514 ; 0.19	3	0.165 ; 2	75 ; 68%	557 $[M+H]^+$

Chromato. - EtOAc

^1H NMR spectrum (DMSO d_6) : 1.12 (d, 3H) ; 1.25 (s, 6H) ; 1.32 (m, 2H) ; 1.42 (m, 4H) ; 1.50 ; (m,2H) ; 1.61 (m, 4H) ; 2.28 (s, 6H) ; 2.35-2.85 (m, 7H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 7.01 (s, 1H) ; 7.06 (s, 2H) ; 7.15 (m, 3H) ; 7.24 (m, 2H) ; 11.8 (s br 1H).

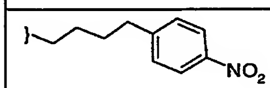
Example 4.5

R	CR5 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	1600; 0.5	30	0.58;7	185 ; 63%	587 [M+H]+

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.35 (m, 2H) ; 1.44(m, 4H) ; 1.47 ; (m,2H) ; 1.61 (m, 4H) ; 2.29 (s, 6H) ; 2.4-2.9 (m, 7H) ; 3.70 (s, 3H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 6.81 (d, 2H) ; 7.04 (m, 5H) ; 11.8 (s br 1H).

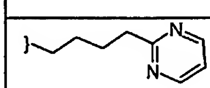
Example 4.6

R	CR6 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	230 ; 0.23	5	0.19 ; 2.3	103 ;56%	xxx [M+H] +

Chromato. - $EtOAc/CH_2Cl_2$ (75 to 100% EtOAc) and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH).

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.37 (m, 2H) ; 1.42 (m, 4H) ; 1.54 (m, 2H) ; 1.59 (m, 4H) ; 2.28 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 7.02 (s, 1H) ; 7.05 (s, 2H) ; 7.44 (d, 2H) ; 8.14 (d,2H) ; 11.8 (s br 1H)..

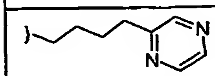
Example 4.7

R	CR7 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.23	5	0.19 ; 2.3	48 ; 37%	559 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.17 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.48 (m, 2H) ; 1.61 (m, 4H) ; 1.71 (m, 2H) ; 2.3 (s, 6H) ; 2.55-3.0 (m, 7H) ; 4.17 (s, 2H) ; 4.58 (s, 2H) ; 7.04 (m, 3H) ; 7.32 (t, 1H) ; 8.71 (d, 2H) ; 11.8 (s br 1H).

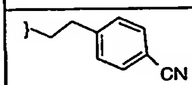
Example 4.8

R	CR8 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.23	3	0.19 ; 2.3	71 ; 54%	559 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 6H) ; 1.63 (m, 6H) ; 2.29 (s, 6H) ; 2.55-2.9 (m, 7H) ; 4.16 (s, 2H) ; 4.57 (s, 2H) ; 7.02 (s, 1H) ; 7.05 (s, 2H) ; 8.45 (d, 1H) ; 8.52 (m, 2H) ; 11.8 (s br 1H)..

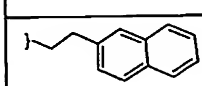
Example 4.9

R	CR9 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.38	10	0.31 ; 3.8	94 ; 45%	554 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d6) : 1.12 (d, 3H) ; 1.24 (s, 6H) ; 1.41 (m, 4H) ; 1.60 (m, 4H) ; 2.29 (s, 6H) ; 2.6-2.9 (m, 7H) ; 4.15 (s, 2H) ; 4.56 (s, 2H) ; 7.02 (s, 3H) ; 7.31 (d, 2H) ; 7.68 (d, 2H) ; 11.8 (s br 1H).

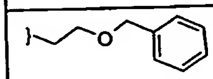
Example 4.10

R	CR10 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.23	3	0.19 ; 2.3	50 ; 38%	579 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 7% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.16 (d, 3H) ; 1.25 (s, 6H) ; 1.40 (m, 4H) ; 1.59 (m, 4H) ; 2.27 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.16 (m, 2H) ; 4.56 (s, 2H) ; 7.03 (s, 1H) ; 7.04 (s, 2H) ; 7.3 (d, 1H) ; 7.46 (m, 2H) ; 7.62 (s, 1H) ; 7.8 (m, 2H) ; 7.86 (d,1H) ; 11.8 (s br 1H).

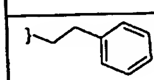
Example 4.11

R	CR11 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.23	3	0.19 ; 2.3	88 ; 68%	559 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.29 (s, 6H) ; 2.6-2.95 (m, 5H) ; 3.45 (s, 2H) ; 4.16 (s,2H) ; 4.41 (s, 2H) ; 4.56 (s, 2H) ; 7.03 (s, 1H) ; 7.06 (s, 2H) ; 7.2-7.35 (m, 5H) ; 11.8 (s br 1H).

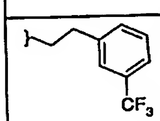
Example 4.12

R	CR12 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.46	10	0.38 ; 4.6	152 ; 62%	529 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.60 (m, 4H) ; 2.29 (s, 6H) ; 2.45-2.95 (m, 7H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 7.03 (s, 1H) ; 7.04 (s, 2H), 7.10 (d, 2H) ; 7.16 (t, 1H) ; 7.24 (t, 2H) ; 11.8 (s br 1H).

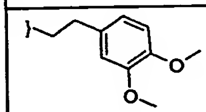
Example 4.13

R	CR13 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.38	20	450 ; 7.6	154 ; 68%	597$[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 7% MeOH)

1H NMR spectrum (DMSO d6) : 1.12 (d, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.6 (m, 4H) ; 2.27 (s, 6H) ; 2.6-2.9 (m, 7H) ; 4.14 (m, 2H) ; 4.56 (s, 2H) ; 7.02 (s, 1H) ; 7.03 (s, 2H) ; 7.45 (m, 4H) ; 11.8 (s br 1H).

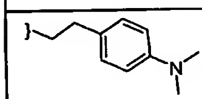
Example 4.14

R	CR14 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	105 ; 71%	589 $[M+H]^+$

Chromato. - EtOAc/CH_2Cl_2 (50 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.60 (m, 4H) ; 2.29 (s, 6H) ; 2.6-2.9 (m, 7H) ; 3.68 (s, 3H) ; 3.70 (s, 3H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 6.60 (q, 1H) ; 6.72 (d, 1H) ; 6.79 (d, 1H) ; 7.03 (s, 1H) ; 7.05 (s, 1H) ; 11.8 (s br 1H).

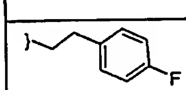
Example 4.15

R	CR15 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.295 ; 5	32 ; 22%	572 $[M+H]^+$

Chromato. - MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.16 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.60 (m, 4H) ; 2.30 (s, 6H) ; 2.6-2.9 (m, 7H) ; 2.83 (s, 6H) ; 4.16 (s, 2H) ; 4.57 (s, 2H) ; 6.61 (d, 2H) ; 6.92 (d, 2H) ; 7.04 (s, 3H) ; 11.8 (s br 1H).

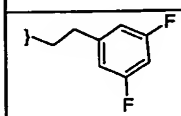
Example 4.16

R	CR16 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.46	10	0.380 ; 4.6	149 ; 59%	547 $[M+H]^+$

Chromato. - EtOAc/CH_2Cl_2 (0 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.60 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 7.03 (m, 5H) ; 7.12 (m, 2H) ; 11.8 (s br 1H).

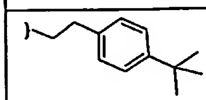
Example 4.17

R	CR18 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	61 ; 43%	565 $[M+H]^+$

Chromato. - EtOAc/CH_2Cl_2 (50 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum ($CDCl_3$) : 1.21 (d, 3H) ; 1.35 (d, 6H) ; 1.44 (m, 4H) ; 1.75 (m, 4H) ; 2.33 (s, 6H) ; 2.6-3.1 (m, 7H) ; 4.26 (m, 2H) ; 4.63 (s, 2H) ; 6.61 (m, 3H) ; 7.01 (s, 3H) ; 9.1 (s br, 1H).

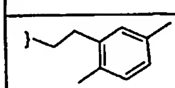
Example 4.18

R	CR19 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	53 ; 36%	585 $[M+H]^+$

Chromato. - MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 15H) ; 1.41 (m, 4H) ; 1.6 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.15 (s, 2H) ; 4.56 (s, 2H) ; 7.02 (d, 2H) ; 7.03 (s, 1H) ; 7.04 (s, 2H) ; 7.25 (d, 2H) ; 11.8 (s br 1H).

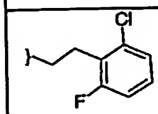
Example 4.19

R	CR20 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	40 ; 29%	557 $[M+H]^+$

Chromato. - MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.18 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.16 (s, 3H) ; 2.20 (s, 3H) ; 2.30 (s, 6H) ; 2.5-2.95 (m, 7H) ; 4.17 (s, 2H) ; 4.56 (s, 2H) ; 6.84 (s, 1H) ; 6.88 (d, 1H) ; 6.99 (s, 1H) ; 7.05 (s, 3H) ; 11.8 (s br 1H).

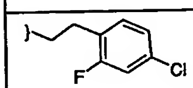
Example 4.20

R	CR21 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	49 ; 34%	581 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.9 (m, 7H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 7.02 (s, 1H) ; 7.04 (s, 2H) ; 7.15 (m, 1H) ; 7.27 (m, 2H) ; 11.8 (s br 1H).

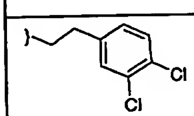
Example 4.21

R	CR22 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	64 ; 44%	581 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.15 (s, 2H) ; 4.56 (s, 2H) ; 7.02 (s, 1H) ; 7.04 (s, 2H) ; 7.10 (m, 1H) ; 7.26 (m, 1H) ; 7.35 (m, 1H) ; 11.8 (s br 1H).

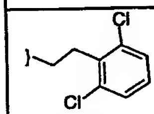
Example 4.22

R	CR23 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	50 ; 34%	597 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.28 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.16 (m, 2H) ; 4.56 (s, 2H) ; 7.03 (s, 3H) ; 7.11 (d, 1H) ; 7.41 (s, 1H) 7.48 (d, 1H) ; 11.8 (s br 1H).

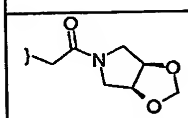
Example 4.23

R	CR24 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	40 ; 27%	597 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.61 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 7.02 (s, 1H) ; 7.05 (s, 2H) ; 7.25 (t, 1H) ; 7.4 (d, 2H) ; 11.8 (s br 1H).

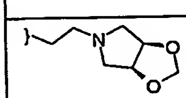
Example 4.24

R	CR25 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.23	5	540 ; 9.2	50 ; 37%	580 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.31 (s, 6H) ; 2.55-2.95 (m, 3H) ; 3.1-3.75 (m, 4H) ; 3.67 (m, 2H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 4.62 (m, 1H) ; 4.68 (m, 1H) ; 4.76 (s, 1H) ; 4.93 (s, 1H) ; 7.03 (s, 1H) ; 7.06 (s, 2H) ; 11.8 (s br 1H).

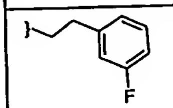
Example 4.25

R	CR26 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.23	5	0.810 ; 13.2	68 ; 52%	566 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.26 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 2.03 (m, 2H) ; 2.31 (s, 6H) ; 2.33 (m, 3H) ; 2.55-2.95 (m, 6H) ; 4.14 (s, 2H) ; 4.49 (m, 2) ; 4.58 (s, 2H) ; 4.71 (s, 1H) ; 4.8 (s, 1H) ; 7.03 (s, 1H) ; 7.06 (s, 2H) ; 11.8 (s br 1H).

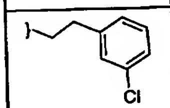
Example 4.26

R	CR27 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.26	5	0.27 ; 3.3	55 ; 38%	547 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 6.97 (m, 3H) ; 7.03 (s, 3H) ; 7.27 (m, 1H) ; 11.8 (s br 1H).

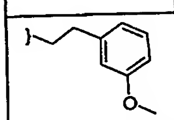
Example 4.27

R	CR28 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.26	5	0.27 ; 3.3	40 ; 27%	563 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.15 (m, 2H) ; 4.57 (s, 2H) ; 7.03 (s, 3H) ; 7.09 (m, 1H) ; 7.25 (m, 3H) ; 11.8 (s br 1H).

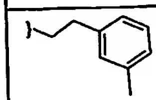
Example 4.28

R	CR29 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.26	5	0.27 ; 3.3	47 ; 32%	559 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.16 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.3 (s, 6H) ; 2.55-2.95 (m, 7H) ; 3.71 (s, 3H) ; 4.16 (s, 2H) ; 4.56 (s, 2H) ; 6.7 (m, 3H) ; 7.04 (s, 3H) ; 7.16 (m, 1H) ; 11.8 (s br 1H).

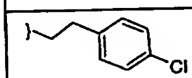
Example 4.29

R	CR30 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.26	5	0.27 ; 3.3	70 ; 49%	543 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.24 (s, 3H) ; 2.3 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.16 (s, 2H) ; 4.57 (s, 2H) ; 6.90 (m, 2H) ; 6.98 (d, 1H) ; 7.04 (s, 3H) ; 7.12 (t, 1H) ; 11.8 (s br 1H).

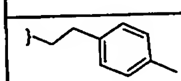
Example 4.30

R	CR31 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.26	5	0.27 ; 3.3	64 ; 43%	563 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (m, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.29 (s, 6H) ; 2.5-2.9 (m, 7H) ; 4.16 (s, 2H) ; 4.56 (m, 2H) ; 7.03 (s, 3H) ; 7.14 (d, 2H) ; 7.29 (d, 2H) ; 11.8 (s br 1H).

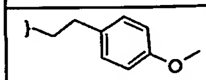
Example 4.31

R	CR32 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.26	5	0.27 ; 3.3	143 ; 100%	543 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (m, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.24 (s, 3H) ; 2.29 (s, 6H) ; 2.5-2.95 (m, 7H) ; 4.15 (s, 2H) ; 4.56 (m, 2H) ; 6.98 (d, 2H) ; 7.04 (m, 5H) ; 11.8 (s br 1H).

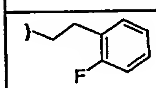
Example 4.32

R	CR33 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.26	5	0.27 ; 3.3	133 ; 90%	559 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (m, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.29 (s, 6H) ; 2.5-2.95 (m, 7H) ; 3.70 (s, 3H) ; 4.15 (s, 2H) ; 4.56 (m, 2H) ; 6.79 (d, 2H) ; 7.01 ; (d, 2H) ; 7.04 (s, 3H) ; 11.8 (s br 1H).

Example 4.33

R	CR34 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.26	5	0.27 ; 3.3	51 ; 35%	547 $[M+H]^+$

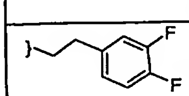
Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (m, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 4H) ; 2.29 (s, 6H) ; 2.5-2.95 (m, 7H) ; 3.70 (s, 3H) ; 4.16 (m, 2H) ; 4.56 (s, 2H) ; 7.04 (s, 3H) ; 7.09 (m, 2H) ; 7.21 ; (m, 2H) ; 11.8 (s br 1H).

Example 4.34

Example **4.34** was prepared by a different methodology (opening of epoxide by **Ce**) : see below.

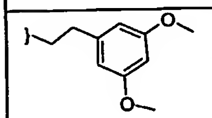
Example 4.35

R	CR36 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	78 ; 55%	565 $[M+H]^+$

Chromato. - $EtOAc/CH_2Cl_2$ (50 to 100% EtOAc) and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.14 (m, 2H) ; 4.57 (s, 2H) ; 6.94 (m, 1H) ; 7.03 (s, 3H) ; 7.15 (m, 1H) ; 7.26 (m, 1H) ; 11.8 (s br 1H).

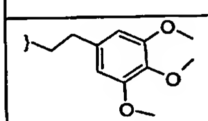
Example 4.36

R	CR37 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	32 ; 22%	589 $[M+H]^+$

Chromato. - EtOAc/CH_2Cl_2 (50 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.60 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 7H) ; 3.68 (s, 6H) ; 4.15 (m, 2H) ; 4.57 (s, 2H) ; 6.3 (m, 3H) ; 7.03 (s, 1H) ; 7.04 (s, 2H) ; 11.8 (s br 1H).

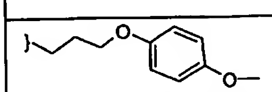
Example 4.37

R	CR38 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	102 ; 66%	619 $[M+H]^+$

Chromato. - EtOAc/CH_2Cl_2 (50 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.60 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 7H) ; 3.60 (s, 3H) ; 3.69 (s, 6H) ; 4.14 (s, 2H) ; 4.56 (s, 2H) ; 6.42 (s, 2H) ; 7.02 (s, 1H) ; 7.05 (s, 2H) ; 11.8 (s br 1H) .

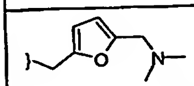
Example 4.38

R	CR39 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	91 ; 62%	589 $[M^+H]^+$

Chromato. - EtOAc/CH2C12 (50 to 100% EtOAc) and then MeOH/CH2C12 (0 to 10% MeOH)

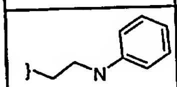
1H NMR spectrum (DMSO d6) : 1.15 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 1.78 (m,2H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 5H) ; 3.68 (s, 3H) ; 3.88 (t, 2H) ; 4.15 (s, 2H) ; 4.56 (s, 2H) ; 6.80 (m, 4H) ; 7.02 (s, 1H) ; 7.06 (s, 2H) ; 11.8 (s br 1H).

Example 4.39

R	CR40 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	85 ; 61%	562 $[M+H]^+$

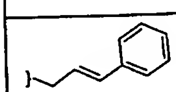
Chromato. - $EtOAc/CH_2Cl_2$ (50 to 100% EtOAc) and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH).
^{1}H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.08 (s, 6H) ; 2.30 (s, 6H) ; 2.55-2.95 (m, 3H) ; 3.35 (s, 2H) ; 3.53 (s, 2H) ; 4.14 (m, 2H) ; 4.57 (s, 2H) ; 6.01 (d, 1H) ; 6.10 (d, 1H) ; 7.03 (s, 1H) ; 7.05 (s, 2H) , 11.8 (s br 1H).

Example 4.40

R	CR41 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	40 ; 29%	544 $[M+H]^+$

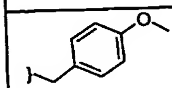
Chromato. - $EtOAc/CH_2Cl_2$ (50 to 100% EtOAc) and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)
^{1}H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.61 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 5H) ; 3.01 ; (m, 2H) ; 4.14 (s, 2H) ; 4.56 (s, 2H) ; 5.37 (s, 1H) ; 6.50 (m, 3H) ; 7.04 (m, 5H) ; 11.8 (s br 1H).

Example 4.41

R	CR42 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	87 ; 64%	541 $[M+H]^+$

Chromato. - $EtOAc/CH_2Cl_2$ (50 to 100% EtOAc) and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)
^{1}H NMR spectrum (DMSO d_6) : 1.16 (d, 3H) ; 1.20 (m, 6H) ; 1.41 (m, 4H) ; 1.61 (m, 4H) ; 2.30 (s, 6H) ; 2.55-2.95 (m, 3H) ; 3.27 (m, 2) ; 4.13 (s, 2H) ; 4.53 (s, 2H) ; 6.23 (m, 1H) ; 6.42 (d, 1H) ; 7.04 (s, 1H) ; 7.07 (s, 2H) ; 7.21 (t, 1H) ; 7.30 (t, 2H) ; 7.35 (d, 2H) ; 11.8 (s br 1H).

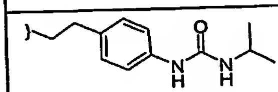
Example 4.42

R	CR43 mg ; mmol Cf	CH2Cl2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 4.5	98 ; 72%	545 $[M+H]^+$

Chromato. - $EtOAc/CH_2Cl_2$ (50 to 100% EtOAc) and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.20 (m, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.31 (s, 6H) ; 2.61 (m, 1H) ; 2.68 (m, 1H) ; 2.85 (m, 1H) ; 3.53 (s, 2H) ; 3.70 (s, 3H) ; 4.12 (m, 2H) ; 4.56 (s, 2H) ; 6.81 (d, 2H) ; 7.03 (s, 1H) ; 7.07 (s, 2H) ; 7.12 (d, 2H) ; 11.8 (s br 1H).

Example 4.43

R	CR44 mg ; mmol Cf	CH2Cl2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.27 ; 3.3	100 ; 63%	629 $[M+H]^+$

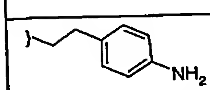
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc) and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum (DMSO d_6) : 1.08 (d, 6H) ; 1.18 (d, 3H) ; 1.26 (s, 6H) ; 1.42 (m, 4H) ; 1.60 (m, 4H) ; 2.31 (s, 6H) ; 2.55-2.95 (m, 7H) ; 3.73 (m, 1H) ; 4.18 (m, 2H) ; 4.56 (s, 2H) ; 5.95 (s, 1H) ; 6.96 (d, 2H) ; 7.04 (s, 3H) ; 7.25 (d, 2H) ; 8.22 (s, 1H) ; 11.8 (s br 1H).

Example 4.44

Example **C45** was prepared by a different methodology (reductive amination of Ce) : see below.

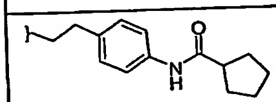
Example 4.45

R	CR46 mg ; mmol Cf	CH2Cl2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	108 ; 0.14	3	0.17 ; 2.0	71 ; 93%	544 $[M+H]^+$

Chromato. - EtOAc and then $MeOH/CH_2Cl_2$ (0 to 15% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.14 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.3 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 4.83 (s, 2H) ; 6.44 (d, 2H) ; 6.74 (d, 2H) ; 7.04 (s, 1H) ; 7.05 (s, 2H) ; 11.8 (s br, 1H).

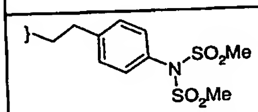
Example 4.46

R	CR47 mg ; mmol	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.14	5	0.15 ; 1.8	41 ; 45%	640 [M+H]$^+$

Chromato. - EtOAc/CH_2Cl_2 (0 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.18 (d, 3H) ; 1.25 (m, 6H) ; 1.42 (m, 4H) ; 1.5-1.9 (m, 12H) ; 2.31 (s, 6H) ; 2.55-2.95 (m, 8H) ; 4.16 (m, 2H) ; 4.56 (s, 2H) ; 7.03 (m, 5H) ; 7.51 (d, 2H) ; 9.81 ; (s, 1H) ; 11.8 (s br, 1H).

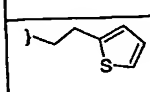
Example 4.47

R	CR48 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.15	3	0.12 ; 1.5	135 ; 99%	700 [M+H]$^+$

Chromato. - EtOAc/CH_2Cl_2 (0 to 100% EtOAc)

^{1}H NMR spectrum (DMSO d_6 – TFAd) : 1.28 (m, 9H) ; 1.43 (m, 4H) ; 1.62 (m, 4H) ; 2.33 (s, 6H) ; 2.8-3.25 (m, 7H) ; 3.51 (s, 6H) ; 4.23 (m, 2H) ; 4.57 (s, 2H) ; 7.05 (s, 2H) ; 7.08 (s, 1H) ; 7.31 (d, 2H) ; 7.47 (d, 2H) ; 11.8 (s br, 1H).

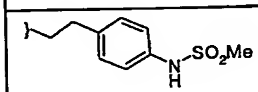
Example 4.48

R	CR49 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	3	0.15 ; 2.5	80 ; 60%	535 [M+H]$^+$

Chromato. - EtOAc/CH_2Cl_2 (0 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.30 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.15 (m, 2H) ; 4.57 (s, 2H) ; 6.76 (d, 1H) ; 6.90 (dd, 1H) ; 7.02 (s, 1H) ; 7.05 (s, 2H) ; 7.27 (d, 1H) ; 11.76 (s br, 1H).

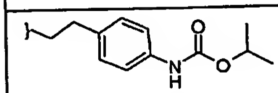
Example 4.49

R	CR50 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.6	5	0.355 ; 6	181 ; 49%	622 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.12 (d, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.60 (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.85 (m, 7H) ; 2.92 (s, 3H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 7.06 (m, 7H) ; 11.74 (s br, 1H).

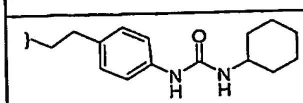
Example 4.50

R	CR51 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.15	3	0.09 ; 1.5	63 ; 67%	630 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.16 (d, 3H) ; 1.25 (m, 12H) ; 1.42 (m, 4H) ; 1.60 (m, 4H) ; 2.30 (s, 6H) ; 2.55-2.95 (m, 7H) ; 4.16 (m, 2H) ; 4.5 (s, 2H) ; 4.87 ; (m, 1H) ; 7.0 (d, 2H) ; 7.04 (s, 3H) ; 7.34 (s, 2H) ; 9.44 (s, 1H) ; 11.8 (s br, 1H).

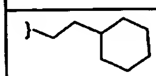
Example 4.51

R	CR52 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.11	2	0.065 ; 1.1	42 ; 57%	669 $[M+H]^+$

Chromato. - $MeOH/CH_2Cl_2$ (0 to 15% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.16 (d, 3H) ; 1.25 (s, 6H) ; 1.25-1.8 (m, 18H) ; 2.31 (s, 6H) ; 2.55-2.95 (m, 7H) ; 3.43 (m, 1H) ; 4.16 (m, 2H) ; 4.56 (s, 2H) ; 6.04 (s, 1H) ; 6.96 (d, 2H) ; 7.04 (s, 3H) ; 7.25 (d, 2H) ; 8.25 (s, 1H) ; 11.86 (s br, 1H).

Example 4.52

R	CR53 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.4	5	0.24 ; 4	93 ; 44%	535 $[M+H]^+$

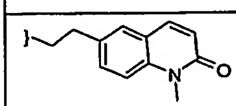
Chromato. – EtOAc

^{1}H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.25 (s, 6H) ; 1.1-1.7 (m, 21H) ; 2.3 (s, 6H) ; 2.35-2.85 (m, 5H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 7.03 (s, 1H) ; 7.06 (s, 2H) 11.8 (s br, 1H).

Example 4.53

Example **4.53** was prepared by a different methodology (alkylation of Ce) : see below

Example 4.54

R	CR55 mg ; mmol Cf	CH_2Cl_2 ml	Propylamine ml ; mmol	Mass mg; Yield	MS-ESI
	nd* ; 0.25	5	0.15 ; 2.5	64 ; 42%	610 $[M+H]^+$

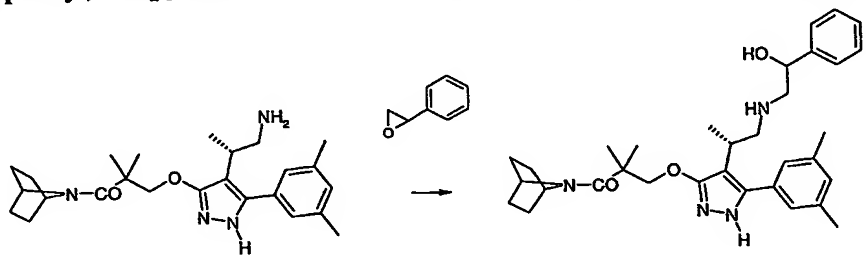
Chromato. - EtOAc and then $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 1.16 (m, 3H) ; 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.59 (m, 4H) ; 2.28 (s, 6H) ; 2.55-3.0 (m, 7H) ; 3.60 (s, 3H) ; 4.16 (s, 2H) ; 4.56 (s, 2H) ; 6.6 (d, 1H) ; 7.02 (s, 3H) ; 7.42 (m, 3H) ; 7.81 (d, 1H) ; 11.8 (s br, 1H).

* nd = not determined, partially purified **CR** used directly from previous step.

Example 4.34

2-[3-(2,2-dimethyl-3-oxo-3-azabicyclo[2.2.1]heptan-7-ylpropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-hydroxy-2-phenylethyl]-(2S)-propylamine



Ce Example 4.34

A solution of Ce (106 mg ; 0.25 mmol) in acetonitrile (3 ml) was treated with styrene oxide and the mixture was heated at 60°C overnight. The solvent was evaporated and the residue purified by flash chromatography eluting with increasingly polar mixtures of $MeOH/CH_2Cl_2$ hexanes (0 to 10% MeOH) to give **Example 4.34** as a white foam (40 mg).

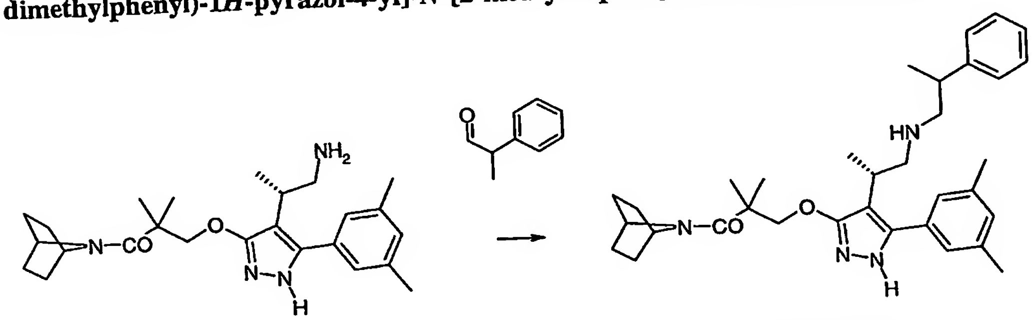
Yield : 30%.

^{1}H NMR spectrum (DMSO d_6) : 1.15 (m, 3H) ; 1.26 (m, 6H) ; 1.42 (m,4H) ; 1.61 ; (m, 4H) ; 2.29 (s, 6H) ; 2.55-2.95 (m, 5H) ; 4.16 (m, 2H) ; 4.57 (m, 3H) ; 7.06 (m, 3H) ; 7.26 (m, 5H) ; 11.6 (s br, 1H).

MS-ESI : 545 $[M+H]^+$

Example 4.44

2-[3-(2,2-dimethyl-3-oxo-3-azabicyclo[2.2.1]heptan-7-ylpropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-methyl-2-phenylethyl]-(2S)-propylamine



Ce

Example 4.44

A solution of Ce (126 mg ; 0.3 mmol) and 2-phenyl propionaldehyde (45 µl ; 0.3 mmol) in methanol (6 ml) under argon was cooled to 0°C. Sodium cyanoborohydride (39 mg ; 0.6 mmol) was added portionwise and the mixture was stirred for 3 h. The methanol was evaporated and the residue taken up in CH_2Cl_2.The organic phase was washed with sat. aq. $NaHCO_3$, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 100% EtOAc) and then MeOH/CH_2Cl_2 (0 to 10% MeOH) to give **Example 4.44** as a white foam (88 mg).

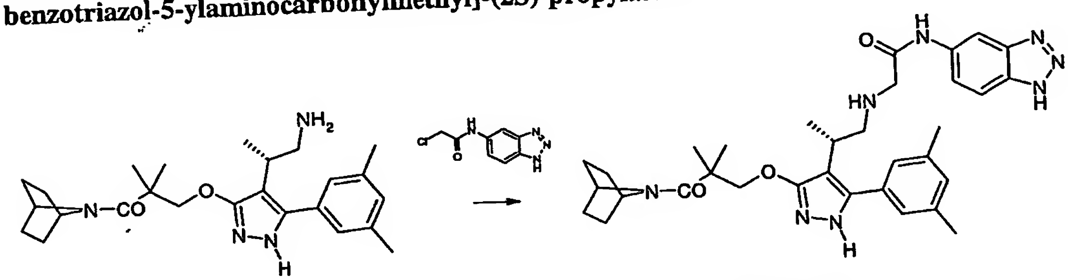
Yield : 54%.

^{1}H NMR spectrum (DMSO d_6) : 1.10 (m, 6H) ; 1.24 (s, 6H) ; 1.41 (m, 4H) ; 1.60 (m, 4H) ; 2.28 (m, 6H) ; 2.55-2.95 (m, 6H) ; 4.14 (s, 2H) ; 4.56 (s, 2H) ; 7.03 (s, 3H) ; 7.09 (t, 2H) ; 7.16 (d, 1H) ; 7.23 (t, 2H) ; 11.8 (s br 1H).

MS-ESI : 543 $[M+H]^+$

Example 4.53

2-[3-(2,2-dimethyl-3-oxo-3-azabicyclo[2.2.1]heptan-7-ylpropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[1*H*-1,2,3-benzotriazol-5-ylaminocarbonylmethyl]-(2S)-propylamine



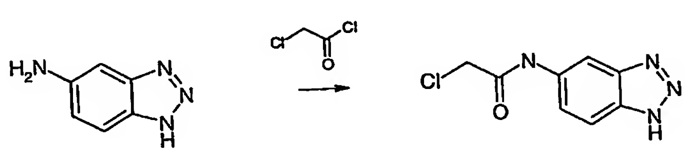
Ce   Example 4.53

To a solution of Ce (200 mg ; 0.47 mmol) in DMA (1 ml) at 140°C was added solid *N*-1*H*-1,2,3-benzotriazole-5-yl-2-chloroacetamide (98 mg ; 0.47 mmol) over 5 min. The reaction mixture was heated at 140°C for a further 5 min. The resulting orange solution was allowed to cool to room temperature and purified by flash chromatography on silica gel eluting with CH_2Cl_2/NH_3 in MeOH (0 to 5% NH_3 in MeOH) to give **Example 4.53** (110 mg).

Yield : 37%

^{1}H NMR spectrum ($CDCl_3$) : 1.20 (d, 3H) ; 1.22 (s, 6H) ; 1.40 (m, 4H) ; 1.70 (m, 4H) ; 2.31 (s, 6H) ; 2.77 (m, 1H) ; 2.99 (m, 2H) ; 3.34 (s, 2H), 4.28 (m, 2H) ; 4.57 (s, 2H) ; 5.37 (s, 1H) ; 6.95 (s, 2H) ; 7.02 (s, 1H) ; 7.17 (br d, 1H) ; 7.84 (br d, 1H) ; 8.26 (s, 1H) ; 9.50 (br s, 1H) ; 9.67 (s, 1H).

MS-ESI : 599 $[M+H]^+$



To a stirred solution of 5-aminobenzotriazole (1.00 g ; 7.50 mmol) in THF (20 ml) at -10°C, were added triethylamine (0.987 g ; 9.75 mmol) and chloroacetyl chloride (0.841 g; 7.50

mmol) dropwise over 5 min. The reaction mixture was allowed to warm to room temperature and stirred overnight.

The resulting precipitate was collected by filtration, washed with CH_2Cl_2 and dried to afford *N*-1*H*-1,2,3-benzotriazole-5-yl-2-chloroacetamide (1.32 g) as a beige solid.

Yield : 83.5%

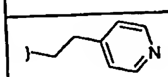
^{1}H NMR spectrum (DMSO d_6) : 4.33 (s, 2H) ; 7.42 (br d, 1H) ; 7.91 (br d, 1H) ; 8.35 (s, 1H) .

MS-ESI : 211 $[M+H]^+$

Intermediates for Examples 4.1-4.55, CR1-CR55 respectively

Starting materials **CR1-CR55** were prepared as follows, the table showing the reaction conditions and characteristics for each example, corresponding to the description of **Example 4** given above:-

CR1

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DEAD mg ; mmol	Mass mg	MS-ESI
	200 ; 0.3	44 ; 0.36	470 ; 1.8	170 ; 1.2	188	760 $[M+H]^+$

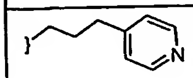
Chromato. - EtOAc/CH_2Cl_2 (0 to 100% EtOAc).

CR2

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DEAD mg ; mmol	Mass mg	MS-ESI
	200 ; 0.3	56 ; 0.37	470 ; 1.8	170 ; 1.2	202	788 $[M+H]^+$

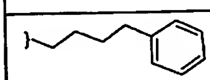
Chromato. - EtOAc/CH_2Cl_2 (50 to 100% EtOAc).

CR3

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DEAD mg ; mmol	Mass mg	MS-ESI
	80 ; 0.12	20 ; 0.15	192 ; 0.73	70 ; 0.49	68	774 $[M+H]^+$

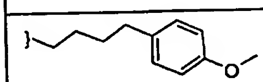
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc).

CR4

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DEAD mg ; mmol	Mass mg	MS-ESI
	130 ; 0.2	36 ; 0.24	300 ; 1.13	100 ; 0.7	514	787 $[M+H]^+$

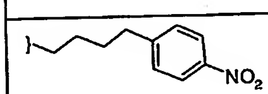
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 40% EtOAc)

CR5

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	327 ; 0.5	100 ; 0.6	786 ; 3	460 ; 2	nd*	nd*

Chromato. - $EtOAc/CH_2Cl_2$ (0 to 50% EtOAc).

CR6

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DEAD mg ; mmol	Mass mg	MS-ESI
	150 ; 0.23	53 ; 0.27	361 ; 1.38	0.145 ; 0.92	230	832 $[M+H]^+$

Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc).

CR7

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DEAD mg ; mmol	Mass mg	MS-ESI
	150 ; 0.23	42 ; 0.27	361 ; 1.38	0.145 ; 0.92	nd*	789 $[M+H]^+$

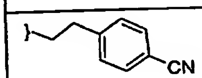
Chromato. - EtOAc

CR8

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DEAD mg ; mmol	Mass mg	MS-ESI
	150 ; 0.23	42 ; 0.27	360 ; 138	0.15 ; 90	nd*	789 $[M+H]^+$

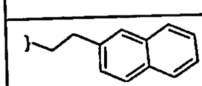
Chromato. - EtOAc/CH_2Cl_2 (0 to 100% EtOAc)

CR9

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DEAD mg ; mmol	Mass mg	MS-ESI
	nd* ; 0.38	81 ; 0.55	724 ; 2.76	0.245 ; 1.55	94 ; 45%	nd*

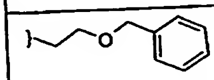
Chromato. - EtOAc

CR10

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	150 ; 0.23	47 ; 0.27	361 ; 1.38	212 ; 0.93	nd*	809 $[M+H]^+$

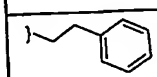
Chromato. - EtOAc/CH_2Cl_2 (0 to 70% EtOAc).

CR11

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	150 ; 0.23	42 ; 0.27	361 ; 1.38	212 ; 0.93	nd*	789 $[M+H]^+$

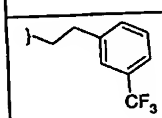
Chromato. - EtOAc/CH_2Cl_2 (0 to 70% EtOAc).

CR12

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	300 ; 0.46	73 ; 0.6	723 ; 2.76	423 ; 1.84	nd*	nd*

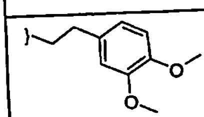
Chromato. - EtOAc/CH_2Cl_2 (0 to 30% EtOAc).

CR13

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	250 ; 0.38	95 ; 0.5	600 ; 2.28	350 ; 1.52	nd*	nd*

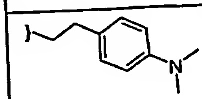
Chromato. - EtOAc/CH_2Cl_2 (0 to 40% EtOAc).

CR14

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	55 ; 0.3	362 ; 1.38	212 ; 0.92	nd*	nd*

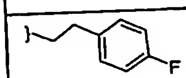
Chromato. - EtOAc/CH_2Cl_2 (0 to 70% EtOAc)

CR15

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	49 ; 0.3	362 ; 1.38	212 ; 0.92	nd*	nd*

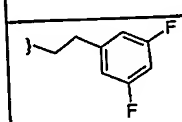
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc)

CR16

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	300 ; 0.46	84 ; 0.6	723 ; 2.76	423 ; 1.84	nd*	777 $[M+H]^+$

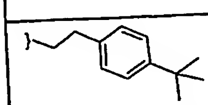
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 20 EtOAc).

CR18

Cgx	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	150 ; 0.23	50 ; 0.3	367 ; 1.4	212 ; 0.92	40	nd*

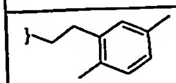
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 20% EtOAc)

CR19

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	163 ; 0.25	57 ; 0.32	393 ; 1.5	230 ; 1.0	nd*	nd*

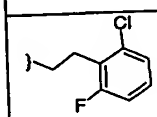
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 20% EtOAc)

CR20

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	163 ; 0.25	48 ; 0.32	393 ; 1.5	230 ; 1.0	nd*	nd*

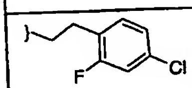
Chromato. - EtOAc/CH_2Cl_2 (0 to 20% EtOAc)

CR21

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	163 ; 0.25	56 ; 0.32	393 ; 1.5	230 ; 1.0	nd*	nd*

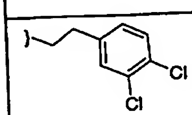
Chromato. - EtOAc/CH_2Cl_2 (0 to 20% EtOAc)

CR22

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	163 ; 0.25	56 ; 0.32	393 ; 1.5	230 ; 1.0	nd*	nd*

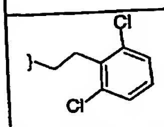
Chromato. - EtOAc/CH_2Cl_2 (0 to 20% EtOAc)

CR23

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	163 ; 0.25	61 ; 0.32	393 ; 1.5	230 ; 1.0	nd*	nd*

Chromato. - EtOAc/CH_2Cl_2 (0 to 20% EtOAc)

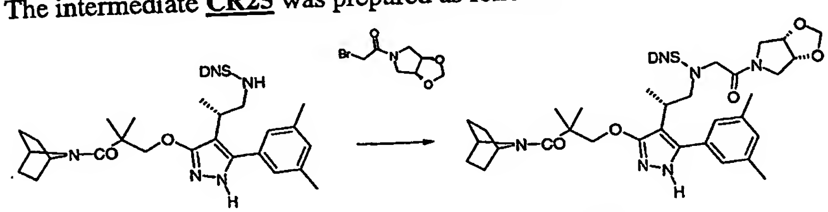
CR24

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	163 ; 0.25	61 ; 0.32	393 ; 1.5	230 ; 1.0	nd*	nd*

Chromato. - $EtOAc/CH_2Cl_2$ (0 to 20% EtOAc)

CR25

The intermediate **CR25** was prepared as follows:-

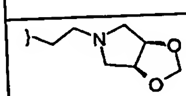


CR25

Cf

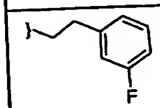
A solution of **Cf** (150 mg ; 0.23 mmol) in DMF (3 ml) was cooled to 0°C and treated with potassium *t*-butoxide (40 mg). The bromomethyl amide (82 mg ; 0.35 mmol) was added and the mixture allowed to warm to room temperature for 1 h. The mixture was treated with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with water, brine and dried over $MgSO_4$. The crude product was used directly in the final step.

CR26

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	150 ; 0.23	48 ; 0.3	367 ; 1.4	212 ; 0.92	nd*	nd*

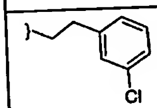
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 20 EtOAc).

CR27

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	173 ; 0.26	45 ; 0.32	415 ; 1.58	243 ; 1.06	nd*	nd*

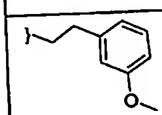
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 20 EtOAc).

CR28

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	173 ; 0.26	50 ; 0.32	415 ; 1.58	243 ; 1.06	nd*	nd*

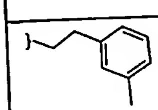
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 20 EtOAc).

CR29

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	173 ; 0.26	49 ; 0.32	415 ; 1.58	243 ; 1.06	nd*	nd*

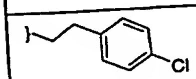
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 20 EtOAc).

CR30

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	173 ; 0.26	44 ; 0.32	415 ; 1.58	243 ; 1.06	nd*	nd*

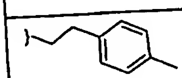
Chromato. - $EtOAc/CH_2Cl_2$ (0 to 20 EtOAc).

CR31

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	173 ; 0.26	50 ; 0.32	415 ; 1.58	243 ; 1.06	nd*	nd*

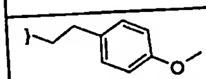
Chromato. - EtOAc/CH_2Cl_2 (0 to 20 EtOAc).

CR32

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	173 ; 0.26	44 ; 0.32	415 ; 1.58	243 ; 1.06	nd*	nd*

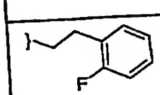
Chromato. - EtOAc/CH_2Cl_2 (0 to 20 EtOAc).

CR33

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	173 ; 0.26	49 ; 0.32	415 ; 1.58	243 ; 1.06	nd*	nd*

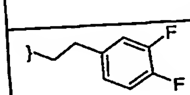
Chromato. - EtOAc/CH_2Cl_2 (0 to 20 EtOAc).

CR34

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	173 ; 0.26	45 ; 0.32	415 ; 1.58	243 ; 1.06	nd*	nd*

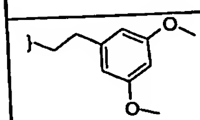
Chromato. - EtOAc/CH_2Cl_2 (0 to 20 EtOAc).

CR36

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	52 ; 0.33	393 ; 1.5	230 ; 1	nd*	nd*

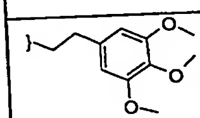
Chromato. - EtOAc/CH_2Cl_2 (10 to 50 EtOAc).

CR37

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	60 ; 0.33	393 ; 1.5	230 ; 1	nd*	nd*

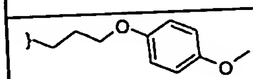
Chromato. - EtOAc/CH_2Cl_2 (10 to 50 EtOAc).

CR38

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	70 ; 0.33	393 ; 1.5	230 ; 1	nd*	nd*

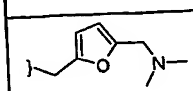
Chromato. - EtOAc/CH_2Cl_2 (10 to 50 EtOAc).

CR39

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	60 ; 0.33	393 ; 1.5	230 ; 1	nd*	nd*

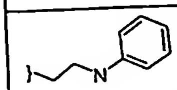
Chromato. - EtOAc/CH_2Cl_2 (10 to 50 EtOAc).

CR40

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	63 ; 0.33	393 ; 1.5	230 ; 1	nd*	nd*

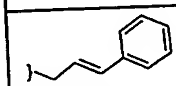
Chromato. - EtOAc/CH_2Cl_2 (10 to 50 EtOAc).

CR41

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	45 ; 0.33	393 ; 1.5	230 ; 1	nd*	nd*

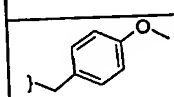
Chromato. - $EtOAc/CH_2Cl_2$ (10 to 50 EtOAc).

CR42

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	44 ; 0.33	393 ; 1.5	230 ; 1	nd*	nd*

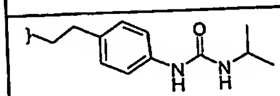
Chromato. - $EtOAc/CH_2Cl_2$ (10 to 50 EtOAc).

CR43

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	46 ; 0.33	393 ; 1.5	230 ; 1	nd*	nd*

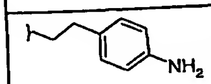
Chromato. - $EtOAc/CH_2Cl_2$ (10 to 50 EtOAc).

CR44

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	75 ; 0.33	393 ; 1.5	230 ; 1	nd*	859 $[M+H]^+$

Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc)

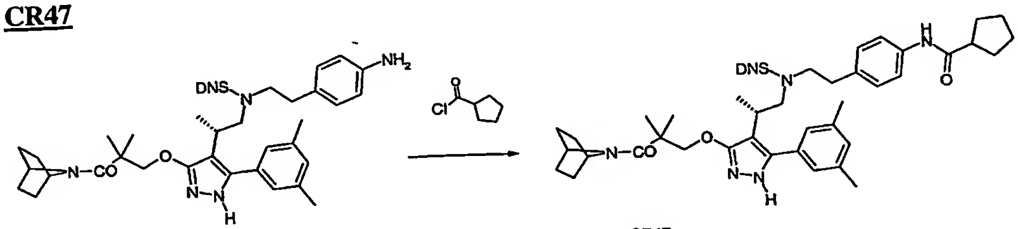
CR45

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	410 ; 0.62	130 ; 0.94	975 ; 3.72	570 ; 2.48	458 (95%)	774 $[M+H]^+$

Chromato. - EtOAc/CH_2Cl_2 (0 to 100% EtOAc)

^{1}H NMR spectrum (DMSO d_6) : 1.16 (d, 3H) ; 1.28 (s, 6H) ; 1.42 (m, 4H) ; 1.60 (m, 4H) ; 2.28 (s, 6H) ; 2.40 (m, 2H) ; 3.06 (m, 1H) ; 3.18 (m, 2H) ; 3.45-3.75 (m, 2H) ; 4.17 (dd, 2H) ; 4.56 (s, 2H) ; 4.86 (s, 2H) ; 6.37 (d, 2H) ; 6.61 (d, 2H) ; 7.01 (s, 3H) ; 8.08 (d, 1H) ; 8.43 (dd, 1H) ; 8.86 (d, 1H) ; 11.8 (s br, 1H).

CR47

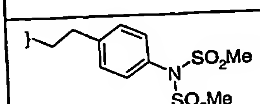


CR46 CR47

A solution of **CR46** (108 mg ; 0.14 mmol) in CH_2Cl_2 (2 ml)was cooled to 0°C and treated with DIEA (27 μl ; 0.154 mmol). A solution of the acid chloride (14 μl ; 0.11 mmol) in CH_2Cl_2 (1 ml) was added and the mixture allowed to warm to room temperature. The crude mixture was deprotected as described for **C47** above.

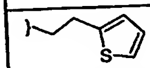
CR48

This intermediate was prepared using a method analogous to the preparation of CR47.

R	Cg46 mg ; mmol	DIEA μl ; mmol	Acid chloride μl ; mmol	CH_2Cl_2	Mass mg	MS-ESI
	120 ; 0.15	29 ; 0.16	30 ; 0.36	3	nd*	nd*

Chromato. - EtOAc

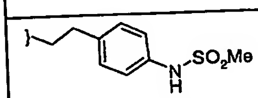
CR49

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	50 ; 0.37	393 ; 1.5	230 ; 1	nd*	nd*

Chromato. - $EtOAc/CH_2Cl_2$ (0 to 50% EtOAc)

CR50

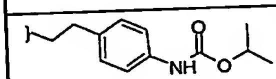
This intermediate was prepared using a method analogous to the preparation of CR47.

R	CR46 mg ; mmol	DIEA μl ; mmol	Acid chloride μl ; mmol	CH_2Cl_2	Mass mg	MS-ESI
	630 ; 0.6	315 ; 1.8	95 ; 1.2	50	nd*	nd*

Chromato. - $EtOAc/CH_2Cl_2$ (0 to 100% EtOAc)

CR51

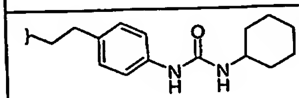
This intermediate was prepared using a method analogous to the preparation of CR47.

R	CR46 mg ; mmol	DIEA μl ; mmol	Acid chloride μl ; mmol	CH_2Cl_2	Mass mg	MS-ESI
	120 ; 0.15	100 ; 0.6	300 1M ; 0.15	3	nd*	860 $[M+H]^+$

Chromato. - $EtOAc/CH_2Cl_2$ (0 to 50% EtOAc)

CR52

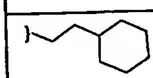
This intermediate was prepared using a method analogous to the preparation of CR47.

R	CR46 mg ; mmol	DIEA μl ; mmol	Acid chloride** μl ; mmol	CH_2Cl_2	Mass mg	MS-ESI
	88 ; 0.11	100 ; 0.6	50 ; 0.4	10	nd*	nd*

Chromato. - EtOAc/CH_2Cl_2 (0 to 50% EtOAc)

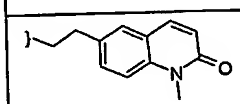
** Cyclohexyl isocyanate was used in place of the corresponding acid chloride.

CR53

R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	262 ; 0.4	102 ; 0.8	629 ; 2.4	368 ; 1.6	nd*	nd*

Chromato. - EtOAc/CH_2Cl_2 (0 to 20% EtOAc)

CR55

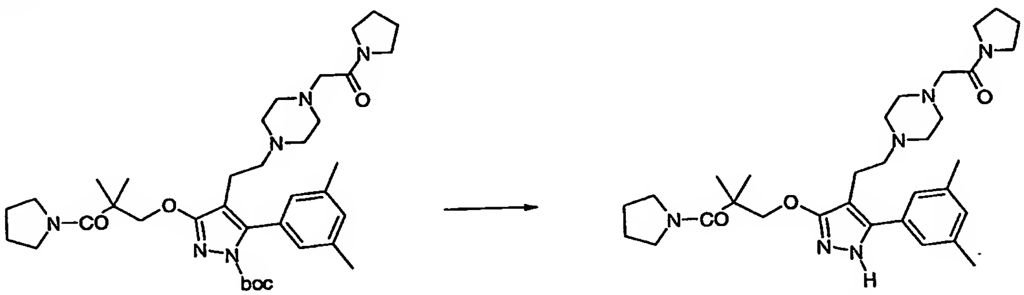
R	Cf mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	Mass mg	MS-ESI
	164 ; 0.25	70 ; 0.34	393 ; 1.5	230 ; 1	nd*	840 $[M+H]^+$

Chromato. - EtOAc/CH_2Cl_2 (0 to 20% EtOAc)

* nd = not determined, partially purified Cgx used directly for final step.

Example 5

3-[2,2-dimethyl-3-oxo-3-(pyrrolidin-1-yl)propoxy]-4-[4-(2-pyrrolidin-1-yl-2-oxo-ethyl)piperzin-1-ylethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole



DR1 Example 5

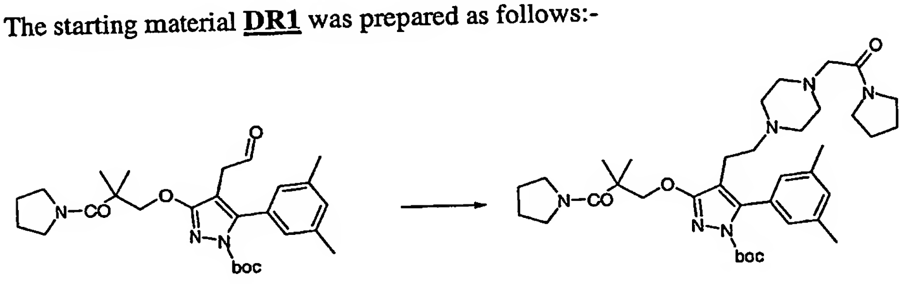
A solution of DR1 (350 mg ; 0.53 mmol) in pyrrolidine (2 ml) was heated at 45°C overnight. The pyrrolidine was evaporated and the residue purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (0 to 7% MeOH) to give **Example 5** as a colourless foam (288 mg).

Yield : 97%

^{1}H NMR spectrum ($CDCl_3$) : 1.38 (s, 6H) ; 1.78 (m, 4H) ; 1.84 (m, 2H) ; 1.94 (m, 2H); 2.35 (s, 6H) ; 2.5-2.7 (m, 12H) ; 3.10 (s, 2H) ; 3.47 (t, 4H) ; 3.58 (m, 4H) ; 4.32 (s, 2H) ; 7.03 (s, 1H) ; 7.27 (s, 2H) ; 8.8 (s br, 1H).

MS-ESI : 565 $[M+H]^+$

The starting material DR1 was prepared as follows:-



DR1

Ab5

A solution of Ab5 (242 mg ; 0.5 mmol) and 4-(4-aminobutyl)-pyridine (125 mg ; 0.65 mmol) in DCE (5 ml) was treated with $NaBH(OAc)_3$ (425 mg ; 2.0 mmol). The mixture was stirred for 20 h and evaporated. The residue was treated with aq. K_2CO_3 (10%) and the mixture

extracted with EtOAc. The organic phase was washed with water, brine and dried over $MgSO_4$. The solution was evaporated to give pure **DR1** as an white solid (350 mg).

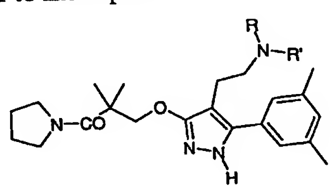
Yield : 100%

^{1}H NMR spectrum ($CDCl_3$) : 1.20 (s, 9H) ; 1.36 (s, 6H) ; 1.74 (s, 4H) ; 1.84 (m, 2H) ; 1.92 (m, 2H) ; 2.31 (s, 6H) ; 2.4-2.6 (m, 12H) ; 3.07 (s, 2H) ; 3.46 (t, 4H) ; 3.57 (m, 4H) ; 4.45 (s, 2H) ; 6.81 (s, 2H) ; 6.98 (s, 1H).

MS-ESI : 665 $[M+H]^+$

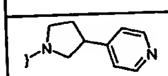
Examples 5.1-5.2

The following Example 5.1 was prepared in a similar manner to Example 5 and Example 5.2 was prepared in a manner similar to Example 2.



the table shows the **NRR'** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of Example 5 given above:-

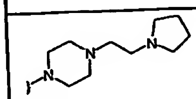
Example 5.1

-NRR'	DR2 mg ; mmol	Pyrrolidine ml ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	85 ; 0.14	2 ; 2.86	White glass	68 ; 96%	516 $[M+H]^+$

Chromato. –$MeOH/CH_2Cl_2$ (7 to 10% MeOH)

^{1}H NMR spectrum ($CDCl_3$) : 1.39 (s, 6H) ; 1.70 (s, 4H) ; 1.83(m, 2H) ; 2.35 (s, 6H) ; 2.5-2.9 (m, 7H) ; 3.0 (m, 1H) ; 3.3 (m, 1H) ; 3.58 (m, 4H) ; 4.34 (dd, 2H) ; 7.03 (s, 1H) ; 7.04 (s, 2H) ; 7.17 (d, 2H) ; 8.48 (d, 2H) ; 8.9 (s br 1H).

Example 5.2

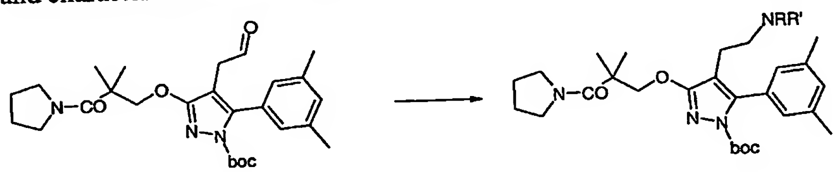
-NRR'	DR3 mg ; mmol	CH_2Cl_2	Prod. Form	Mass mg ; Yield	MS-ESI
	194 ; 0.3	2	White solid	86 ; 52%	551 $[M+H]^+$

Chromato. – LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (0 to 100% H_2O)

^{1}H NMR spectrum ($CDCl_3$) : 1.36 (s, 6H) ; 1.74 (m, 4H) ; 1.83(m, 4H) ; 2.32 (s, 6H) ; 2.4-2.7 (m, 20H) ; 3.56 (m, 4H) ; 4.30 (s, 2H) ; 7.01 (s, 1H) ; 7.02 (s, 2H) ; 8.8 (s br 1H).

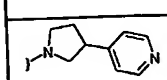
Intermediates for Examples 5.1-5.2, DR2 – DR3 respectively

Starting materials **DR2-3** were prepared as follows, the table showing the reaction conditions and characteristics for each example, corresponding to the description of **DR1** given above:-



Ab5 DR

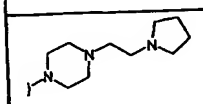
DR2

-NRR'	Ab5 mg ; mmol	Amine mg ; mmol	$NaBH(OAc)_3$ mg ; mmol	Mass mg ; Yield	MS-ESI
	150 ; 0.31	60 ; 0.39	200 ; 0.93	117 ; 61%	616 $[M+H]^+$

Chromato. –EtOAc then MeOH/CH_2Cl_2 (5% MeOH)

^{1}H NMR spectrum ($CDCl_3$) : 1.20 (s, 9H) ; 1.37 (s, 6H) ; 1.70 (s, 4H) ; 1.90 (m, 2H) ; 2.30 (s, 6H) ; 2.4-2.7 (m, 7H) ; 2.9 (m, 1H) ; 3.3 (m, 1H) ; 3.56 (m, 4H) ; 4.47 (dd, 2H) ; 6.80 (s, 2H) ; 6.99 (s, 1H) ; 7.15 (d, 2H) ; 8.48 (d, 2H).

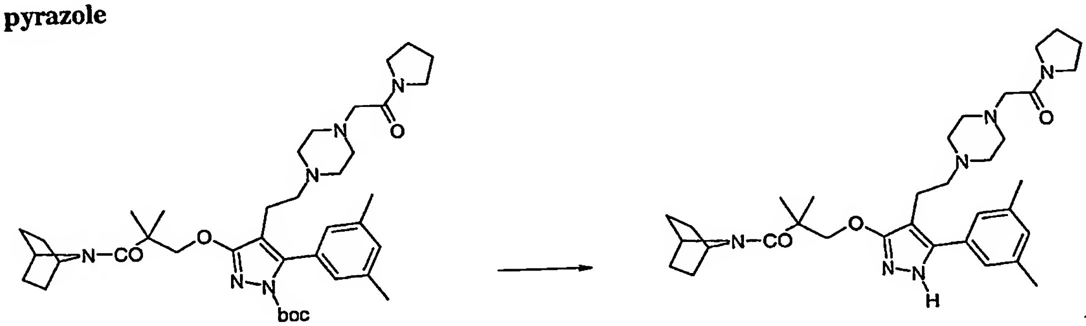
DR3

-NRR'	Ab5 mg ; mmol	Amine mg ; mmol	$NaBH_4$ mg ; mmol	Mass mg ; Yield	MS-ESI
	265 ; 0.55	110 ; 0.6	38 ; 0.6 + AcOH 35 μM	194 ; 54%	651 $[M+H]^+$

Chromato. – Ammonia in MeOH(7<u>N</u>)/CH_2Cl_2 (0 to 10% ammonia in MeOH).

Example 6

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propoxy]-4-[4-(2-pyrrolidin-1-yl-2-oxo-ethyl)piperzin-1-ylethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole



ER1 Example 6

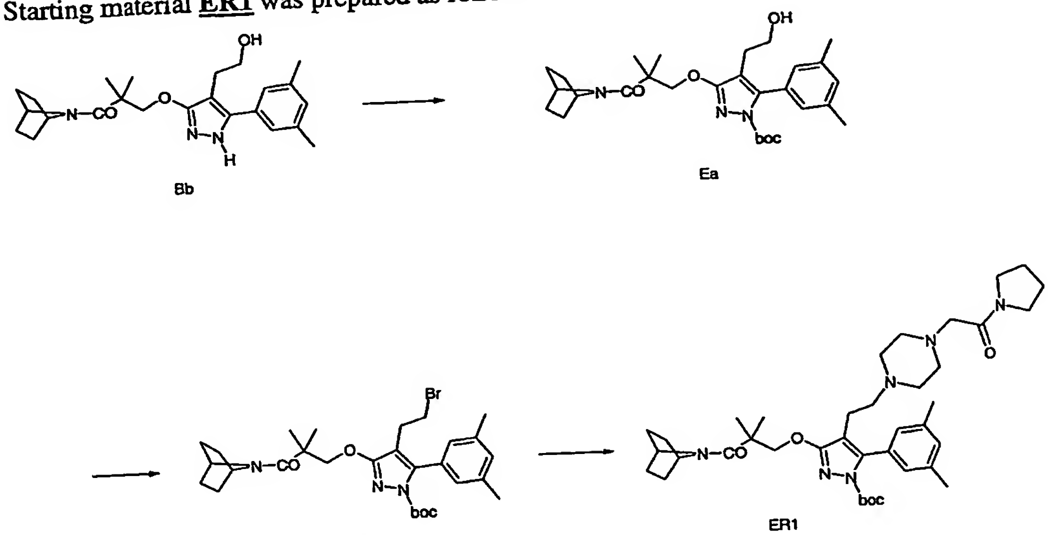
A solution of **<u>ER1</u>** (160 mg ; 0.23 mmol) in pyrrolidine (1 ml) was heated at 45°C overnight. The pyrrolidine was evaporated and the residue purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (5 to 10% MeOH) to give **Example 6** as a white solid (141 mg).

Yield : 100%

^{1}H NMR spectrum ($CDCl_3$) : 1.36 (s, 6H) ; 1.46 (m, 4H) ; 1.77 (m, 4H) ; 1.83 (m, 2H) ; 1.93 (m, 2H) ; 2.35 (s, 6H) ; 2.45-2.65 (m, 12H) ; 3.11 (s, 2H) ; 3.47 (m, 4H) ; 4.28 (s, 2H) ; 4.65 (s, 2H) ; 7.03 (s, 2H) ; 7.26 (s, 1H) ; 8.8 (s br, 1H).

MS-ESI : 591 $[M+H]^+$

Starting material **ER1** was prepared as follows:-



Bb Ea Eb ER1

DMAP (100 mg ; cat.) was added to a solution of **Bb** (4.0 g ; 9.72 mmol) in a mixture of acetonitrile (175 ml) and CH_2Cl_2 (40 ml). The mixture was cooled to –10 °C and a solution of $(BOC)_2O$ (2.54 g ; 11.66 mmol) in CH_2Cl_2 (50 ml) added dropwise during 1.5 h. The mixture was stirred for a further 2.5 h at –10°C to –5°C. Water was added and the mixture stirred overnight at room temperature. The mixture was extracted with CH_2Cl_2 and the organic phase washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (20 to 80% EtOAc) to give the alcohol **Ea** as colourless crystals (2.4 g).

Yield : 48%

^{1}H NMR spectrum ($CDCl_3$) : 1.20 (s, 9H) ; 1.34 (s, 6H) ; 1.45 (m, 4H) ; 1.77 (m, 4H) ; 2.32 (s, 6H) ; 2.42 (t, 2H) ; 3.63 (m, 2H) ; 4.42 (s, 2H) ; 4.65 (s, 2H) ; 6.83 (s, 2H) ; 7.00 (s, 1H)

MS-ESI : 512 $[M+H]^+$

A solution of **Ea** (3.7 g ; 7.23 mmol) and CBr_4 (3.12 g ; 9.4 mmol) in CH_2Cl_2 (150 ml) was cooled to 0°C under argon. Solid PPh_3 (2.84 g ; 10.85 mmol) was added portionwise and the mixture allowed to warm to room temperature overnight. The mixture was directly purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 30% EtOAc) to give the bromide **Eb** as colourless crystals (3.01 g).

Yield : 73%

^{1}H NMR spectrum (DMSO d_6) : 1.51 (s, 9H) ; 1.27 (s, 6H) ; 1.45 (m, 4H) ; 1.63 (m, 4H) ; 2.30 (s, 6H) ; 2.63 (t, 2H) ; 3.51 (t, 2H) ; 4.27 (s, 2H) ; 4.59 (s, 2H) ; 6.93 (s, 2H) ; 7.08 (s, 1H).

MS-ESI : 575 $[M+H]^+$

A mixture of Eb (150 mg ; 0.26 mmol) and 1-(pyrrolidinocarbonylmethyl)piperazine (108 mg ; 0.548 mmol) in acetonitrile (5 ml) under argon was heated at 80°C for 16 h. The solvent was evaporated and the residue was purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (0 to 7% MeOH) to give ER1 as a beige powder (161 mg).

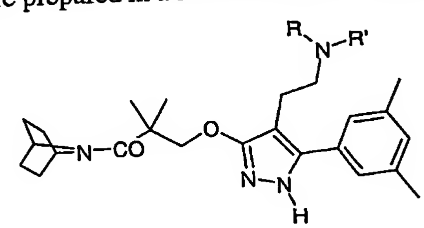
Yield : 89%

^{1}H NMR spectrum ($CDCl_3$) : 1.20 (s, 9H) ; 1.34 (s, 6H) ; 1.46 (m, 4H) ; 1.77 (m, 4H) ; 1.85 (m, 2H) ; 1.94 (m, 2H) ; 2.32 (s, 6H) ; 2.35-2.6 (m, 12H) ; 3.01 (s, 2H) ; 3.46 (m, 4H) ; 4.42 (s, 2H) ; 4.65 (s, 2H) ; 6.82 (s, 2H) ; 7.00 (s, 1H).

MS-ESI : 691 $[M+H]^+$

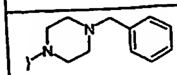
Examples 6.1-6.10

The following examples were prepared in a similar manner to Example 6,



the table shows the **NRR'** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of Example 6 given above. The final two steps were carried out without purification or characterisation of the intermediates <u>ER</u>:-

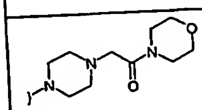
Example 6.1

-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	172 ; 0.3	116 ; 0.66	4	146 ; 85%	570 [M+H]$^+$

Chromato. – Prep. LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O)

^{1}H NMR spectrum (DMSO d_6) : 1.24 (s, 6H) ; 1.41 (m, 4H) ; 1.61 (m, 4H) ; 2.30 (s, 6H) ; 2.3-2.6 (m, 12H) ; 3.43 (s, 2H) ; 4.14 (s, 2H) ; 4.56 (s, 2H) ; 7.01 (s, 1H) ; 7.10 (s, 2H) ; 7.3 (m, 5H) ; 11.7 (s br 1H).

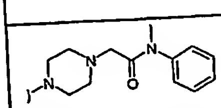
Example 6.2

-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	115 ; 0.2	94 ; 0.44	3	105 ; 87%	607 [M+H]$^+$

Chromato. – Prep. LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (80% H_2O)

^{1}H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.31 (s, 6H) ; 2.3-2.6 (m, 12H) ; 3.10 (s, 2H) ; 3.35-3.6 (m, 8H) ; 4.15 (s, 2H) ; 4.57 (s, 2H) ; 7.02 (s, 1H) ; 7.10 (s, 2H) ; 11.7 (s br 1H).

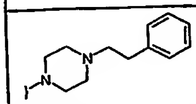
Example 6.3

-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	115 ; 0.2	103 ; 0.44	3	96 ; 77%	627 [M+H]$^+$

Chromato. – Prep. LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (80% H_2O)

^{1}H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.61 (m, 4H) ; 2.30 (s, 6H) ; 2.3-2.6 (m, 12H) ; 2.85 (s br, 2H) ; 3.15 (s br, 3H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 7.01 (s, 1H) ; 7.09 (s, 2H) ; 7.32 (m, 3H) ; 7.41 (m, 2H) ; 11.7 (s br 1H).

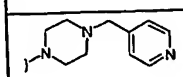
Example 6.4

-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	115 ; 0.2	84 ; 0.44	3	27 ; 25%	584 $[M+H]^+$

Chromato. – Prep. LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O)

^1H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 2.31 (s, 6H) ; 2.3-2.6 (m, 14H) ; 2.70 (t, 2H) ; 4.15 (s, 2H) ; 4.56 (s, 2H) ; 7.02 (s, 1H) ; 7.11 (s, 2H) ; 7.17 (t, 1H) 7.21 (d, 2H) ; 7.26 (t, 2H) ; 11.7 (s br 1H).

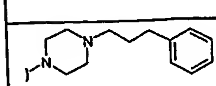
Example 6.5

-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	115 ; 0.2	78 ; 0.44	3	98; 86%	571 $[M+H]^+$

Chromato. – Prep. LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (80% H_2O)

^1H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.41 (m, 4H) ; 1.61 (m, 4H) ; 2.30 (s, 6H) ; 2.3-2.6 (m, 12H) ; 3.48 (s, 2H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 7.01 (s, 1H) ; 7.10 (s, 2H) ; 7.30 (d, 2H) ; 8.49 (dd, 2H) ; 11.7 (s br 1H).

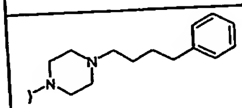
Example 6.6

-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	115 ; 0.2	90 ; 0.44	3	19 ; 16%	598 $[M+H]^+$

Chromato. – Prep. LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O)

^1H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 1.69 (m, 2H) ; 2.23 (t, 2H) ; 2.30 (s, 6H) ; 2.3-2.7 (m, 14H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 7.01 (s, 1H) ; 7.10 (s, 2H) ; 7.17 (m, 3H) ; 7.27 (t, 2H) ; 11.7 (s br 1H).

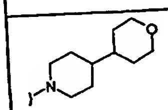
Example 6.7

-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	115 ; 0.2	96 ; 0.44	3	108; 88%	612 $[M+H]^+$

Chromato. – Prep. LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O)

^1H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.42 (m, 6H) ; 1.54 (m, 2H) ; 1.62 (m, 4H) ; 2.23 (t, 2H) ; 2.30 (s, 6H) ; 2.3-2.6 (m, 14H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 7.01 (s, 1H) ; 7.10 (s, 2H) ; 7.17 (m, 3H) ; 7.27 (t, 2H) ; 11.7 (s br 1H).

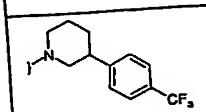
Example 6.8

-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	115 ; 0.2	75 ; 0.44	3	91 ; 81%	563 $[M+H]^+$

Chromato. – Prep. LC/MS H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (80% H_2O)

^1H NMR spectrum (DMSO d_6) : 0.99 (m, 1H) ; 1.15 (m, 3H) ; 1.27 (s, 6H) ; 1.45 (m, 4H) ; 1.55-1.65 (m, 8H) ; 1.85 (t, 2H) ; 2.32 (s, 6H) ; 2.3-2.6 (m, 6H) ; 2.88 (d 2H) ; 3.25 (t, 2H) ; 3.86 (m, 2H) ; 4.16 (s, 2H) ; 4.59 (s, 2H) ; 7.03 (s, 1H) ; 7.12 (s, 2H) ; 11.86 (s br 1H).

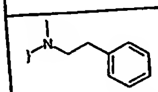
Example 6.9

-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	230 ; 0.4	223 ; 0.84	10	234 ; 94%	623 $[M+H]^+$

Chromato. – $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum ($CDCl_3$) + CD_3OD) : 1.26 (m, 6H) ; 1.37 (m, 4H) ; 1.60 (m, 4H) ; 1.71 (m, 1H) ; 1.97 (m, 2H) ; 2.1 (m, 1H) ; 2.27 (s, 6H) ; 2.8-3.0 (m, 4H) ; 3.15 (m, 2H) ; 3.31 m, 1H) ; 3.61 (m, 2H) ; 4.14 (dd, 2H) ; 4.47 (s, 2H) ; 6.96 (s, 3H) ; 7.36 (d, 2H) ; 7.52 (d, 2H) ; 8.9 (s br, 1H).

Example 6.10

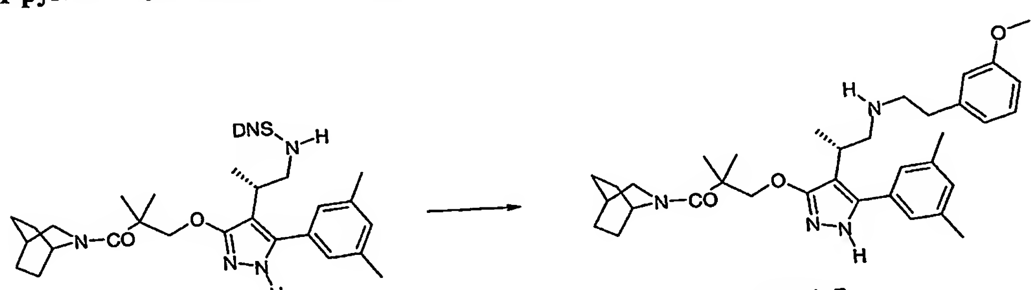
-NRR'	Eb mg ; mmol	Piperazine mg ; mmol	Pyrrolidine ml	Mass mg ; Yield	MS-ESI
	230 ; 0.4	113 ; 0.84	10	166 ; 79%	529 $[M+H]^+$

Chromato. – $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^1H NMR spectrum ($CDCl_3$) : 1.36 (s, 6H) ; 1.43 (m, 4H) ; 1.75 (m, 4H) ; 2.33 (s, 6H) ; 2.39 (s, 3H) ; 2.6-2.8 (m, 8H) ; 4.29 (s, 2H) ; 4.64 (s, 2H) ; 7.02 (s, 1H) ; 7.05 (s, 2H) ; 7.17 (m, 3H) ; 7.26 (m, 2H) ; 8.9 (s br 1H).

Example 7

3-[3-(2,2-dimethyl-3-oxo-3-{azabicyclo[2.2.2]oct-2-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(3-methoxyphenyl)ethyl]-(2S)-propylamine



FR

Example 7

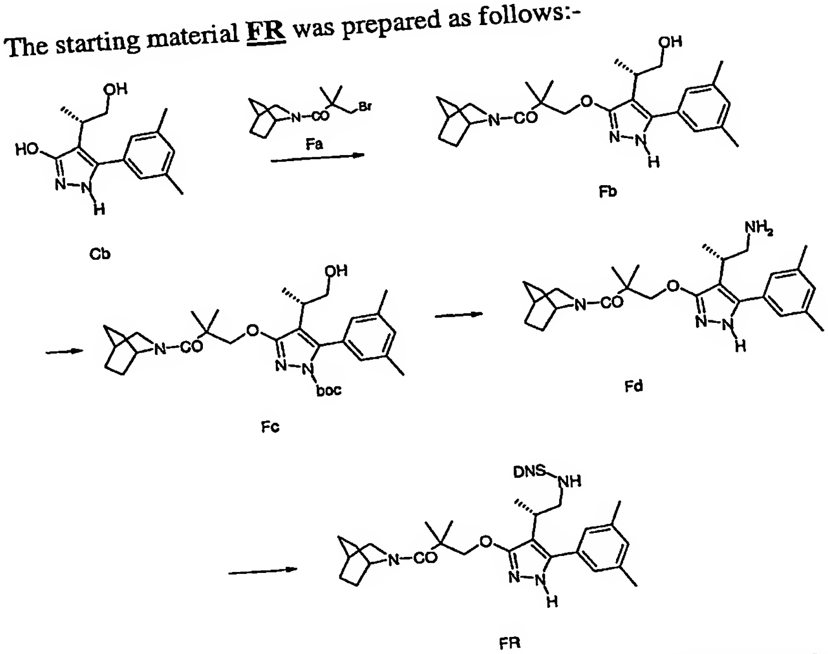
A mixture of **FR** (167 mg ; 0.25 mmol), 3-(2-hydroxyethyl)-methoxybenzene (50 mg ; 0.325 mmol) and triphenylphosphine (393 mg ; 1.5 mmol) in THF (5 ml) at 0°C under argon was treated with DTAD (230 mgl ; 1.0 mmol). The mixture was allowed to warm to room temperature for 1 h when water was added. The mixture was extracted with CH_2Cl_2 and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was taken up directly in CH_2Cl_2 (3 ml) and treated dropwise with n-propylamine (150 μl ; 2.5 mmol). The mixture was stirred at room temperature for 1h and then purified directly by flash chromatography eluting with increasingly polar mixtures of CH_2Cl_2 and then MeOH/CH_2Cl_2 (0 to 10% MeOH) to give **Example 7** as a white foam (100 mg).

Yield : 70%

^{1}H NMR spectrum (DMSO d_6) : 1.15 (d, 3H) ; 1.27 (s, 6H) ; 1.54 (m, 4H) ; 1.67 (m, 4H) ; 1.85 (s, 1H) ; 2.3 (s, 6H) ; 2.55-2.95 (m, 7H) ; 3.24 (m, 2H) ; 3.7 (s, 3H) ; 4.16 (m, 3H) ; 6.7 (m, 3H) ; 7.03 (s, 1H) ; 7.05 (s, 2H) ; 7.15 (t, 1H) ; 11.8 (s br, 1H).

MS-ESI : 573 [M+H]$^+$

The starting material **FR** was prepared as follows:-



This preparation was exactly analogous to that of Examples 4 and 8

Yields and data are given in the following table: -

Compound	Yield	MS-ESI	RMN
Fb	85%	440 $[M+H]^+$	^1H NMR spectrum ($CDCl_3$) : 1.19 (d, 3H) ; 1.36 (s, 3H) ; 1.41 (s, 3H) ; 1.65 (m, 6H) ; 1.83 (m, 2H) ; 1.94 (s, 1H) ; 2.23 (m, 1H) ; 2.35 (s, 6H) ; 3.01 (m, 1H) ; 3.42 (m, 2H) ; 3.69 (m, 1H) ; 3.78 (m, 1H) ; 4.11 (m, 1H) ; 4.21 (m, 1H) ; 4.41 (m, 1H) ; 7.03 (s, 1H) ; 7.05 (s, 2H) ; 8.9 (s br 1H).
Fc	100%	540 $[M+H]^+$	^1H NMR spectrum ($CDCl_3$) : 1.06 (d, 3H) ; 1.19 (s, 9H) ; 1.36 (s, 3H) ; 1.42 (s, 3H) ; 1.56 (m, 6H) ; 1.83 (m, 2H) ; 1.94 (s, 1H) ; 2.25 (m, 1H) ; 2.35 (s, 6H) ; 2.59 (m, 1H) ; 3.41 (m, 2H) ; 3.57 (m, 1H) ; 3.67 (m, 1H) ; 4.11 (m, 1H) ; 4.30 (m, 1H) ; 4.60 (m, 1H) ; 6.84 (s, 2H) ; 7.00 (s, 1H).
Fd	85%	439 $[M+H]^+$	^1H NMR spectrum (DMSO d_6) : 1.16 (d, 3H) ; 1.27 (s, 6H) ; 1.56 (m, 4H) ; 1.68 (m, 4H) ; 1.87 (s, 1H) ; 2.31 (s, 6H) ; 2.36 (m, 2H) ; 2.72 (m, 1H) ; 4.15 (m, 3H) ; 7.02 (s, 1H) ; 7.07 (s, 2H) ; 8.9 (s br 1H).
FR	67%	669 $[M+H]^+$	^1H NMR spectrum (DMSO d_6) : 1.10 (d, 3H) ; 1.25 (s, 6H) ; 1.52 (m, 4H) ; 1.67 (m, 4H) ; 1.83 (s, 1H) ; 2.29 (s, 6H) ; 2.83 (m, 1H) ; 3.19 (m, 2H) ; 4.13 (m, 3H) ; 6.96 (s, 2H) ; 6.98 (s, 1H) ; 8.12 (d, 1H) ; 8.51 (br s, 1H) ; 8.52 (q, 1H) ; 8.79 (d, 1H) ; 11.9 (s br 1H).

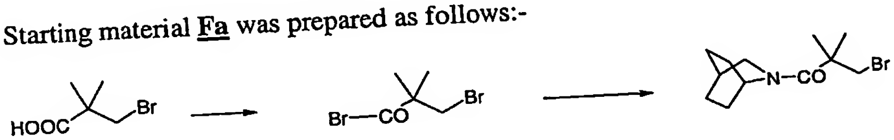
A solution of **Fd** (1.12g ; 2.55 mmol) in CH_2Cl_2 (50 ml) was cooled to 0°C under argon. DIEA (580 μl ; 3.3 mmol) was added followed by a solution of DNOSCl (0.72 g ; 2.68 mmol) in CH_2Cl_2 (10 ml). The mixture was allowed to warm to room temperature for 2 h and was treated with aq. HCl (1N). The mixture was extracted with CH_2Cl_2 and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH_2Cl_2 (0 to 40% EtOAc) to give **FR** as a yellow foam (1.14 g).

Yield : 67%

^{1}H NMR spectrum (DMSO d_6) : 1.10 (d, 3H) ; 1.25 (s, 6H) ; 1.52 (m, 4H) ; 1.67 (m, 4H) ; 1.83 (s, 1H) ; 2.29 (s, 6H) ; 2.83 (m, 1H) ; 3.19 (m, 2H) ; 4.13 (m, 3H) ; 6.96 (s, 2H) ; 6.98 (s, 1H) ; 8.12 (d, 1H) ; 8.51 (br s, 1H) ; 8.52 (q, 1H) ; 8.79 (d, 1H) ; 11.9 (s br 1H).

MS-ESI : 669 $[M+H]^+$

Starting material **Fa** was prepared as follows:-



8 9 Fa

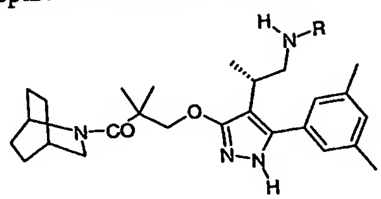
A mixture of **8** (4.0 g ; 22 mmol) and oxalyl bromide (9.5 g ; 44 mmol) containing one drop of DMF was heated at 50°C for 2h and then cooled. The excess of oxalyl bromide was evaporated and the residue azeotroped with toluene to give crude **9** which was taken up directly in CH_2Cl_2 (30 ml) and cooled to 0°C. Diisopropylethylamine (40 ml ; 200 mmol) was added followed by 2.2.2-azabicyclooctane (2.95 g ; 20 mmol) in CH_2Cl_2 (20 ml). The mixture was allowed to warm to room temperature overnight and was diluted with CH_2Cl_2, washed with aq. HCl (2N), aq. NaOH (1N), water, brine and dried over $MgSO_4$. The residue was evaporated to give **Fa** as a beige solid (3.75 g).

Yield : 68%

^{1}H NMR spectrum ($CDCl_3$) : 1.38 (s, 6H) ; 1.67 (m, 6H) ; 1.89 (m, 2H) ; 1.95 (s, 1H) ; 3.40 (m, 2H) ; 3.63 (s, 2H) 4.02 (s, 1H).

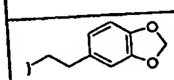
Example 7.1

The following example was prepared in a similar manner to Example 6,



The following example was prepared in a similar manner, the table shows the **NRR'** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of <u>**Example 7**</u> given above:-

<u>**Example 7.1**</u>

-NRR'	FR mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	$nPrNH_2$ µl ; mmol	Mass mg ; Yield
	300 ; 0.45	150 ; 0.9	707 ; 2.7	415 ; 1.8	265 ; 4.5	193 ; 73%

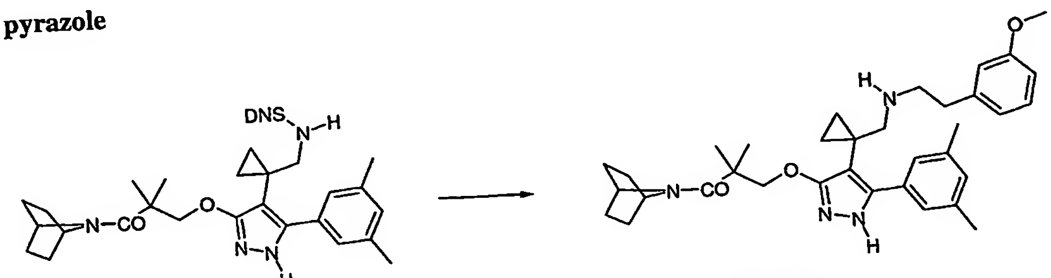
Chromato. – EtOAc

^{1}H NMR spectrum (DMSO d_6) : 1.13 (d, 3H) ; 1.27 (s, 6H) ; 1.55 (m, 4H) ; 1.68 (m, 4H) ; 1.86 (s, 1H) ; 2.3 (s, 6H) ; 2.55-2.95 (m, 7H) ; 3.31 (m, 2H) ; 4.14 (m, 3H) ; 5.93 (s, 2H) ; 6.53 (dd, 1H) ; 6.67 (d, 1H) ; 6.74 (d, 1H) ; 7.02 (s, 1H) ; 7.05 (s, 2H) ; 7.15 (t, 1H) ; 11.74 (s br, 1H).

MS-ESI : 587 $[M+H]^+$

Example 8

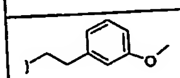
3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propoxy]-4-[1-(3-methoxyphenethylaminomethyl)cycloprop-1-yl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole



Example 8

GR

Example 8 was prepared in a similar manner to Example 7, the table shows the reaction conditions and characteristics corresponding to the description of the preparation of Example 7 given above:-

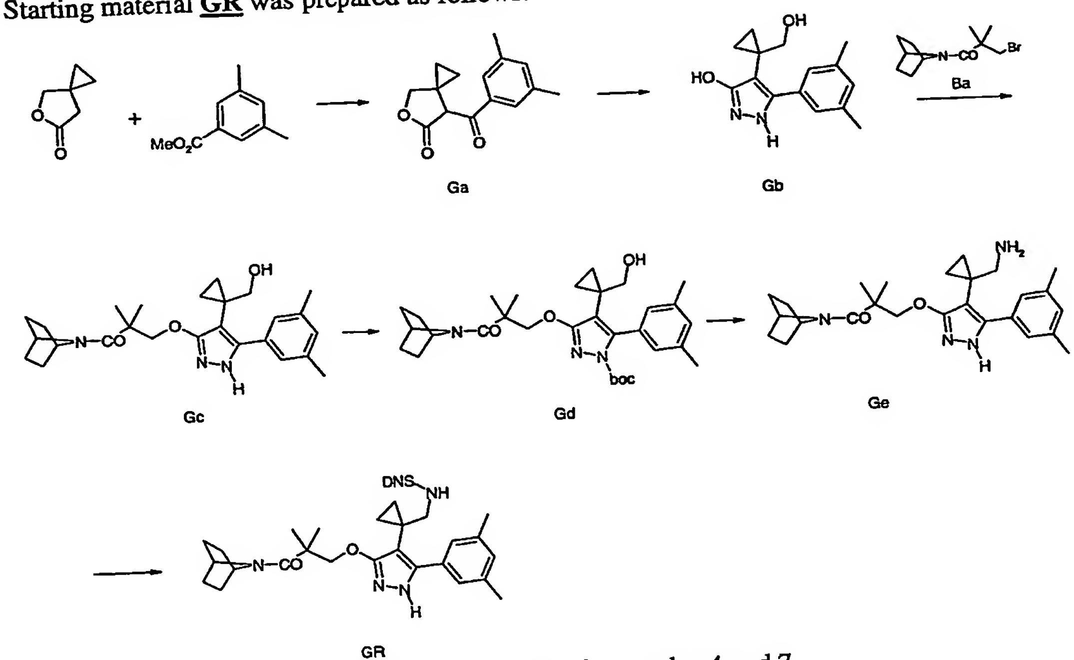
-NRR'	GR mg ; mmol	Alcohol mg ; mmol	Ph_3P mg ; mmol	DTAD mg ; mmol	$nPrNH_2$ µl ; mmol	Mass mg ; Yield
	166 ; 0.25	50 ; 0.33	393 ; 1.5	230 ; 1.0	270 ; 10	68 ; 48%

Chromato. – $MeOH/CH_2Cl_2$ (0 to 10% MeOH)

^{1}H NMR spectrum (DMSO d_6) : 0.42 (m, 2H) ; 0.70 (m, 2H) ; 1.25 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 2.3 (s, 6H) ; 2.6-2.85 (m, 7H) ; 3.69 (s, 3H) ; 4.14 (s, 3H) ; 4.57 (s, 2H) ; 6.71 (m, 3H) ; 7.03 (s, 1H) ; 7.15 (t, 1H) ; 7.33 (s, 2H) ; 11.74 (s br, 1H).

MS-ESI : 571 $[M+H]^+$

Starting material <u>GR</u> was prepared as follows:-



This preparation was exactly analogous to that of examples 4 and 7

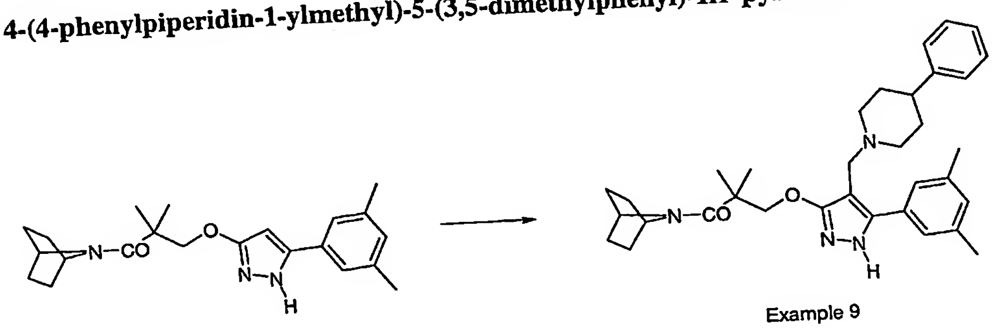
Yields and data are given in the following table: -

Compound	Yield	MS-ESI $[M+H]^+$	RMN
Ga	46%	245	^{1}H NMR spectrum (DMSO d_6) : 0.47 (m, 1H) ; 0.64 (m, 1H) ; 0.85 (m, 1H) ; 0.99 (m, 1H) ; 2.35 (s, 6H) ; 4.11 (d, 1H) ; 4.41 (d, 1H) ; 4.76 (s, 1H) ; 7.36 (s, 1H) ; 7.59 (s, 2H).
Gb	87%	259	^{1}H NMR spectrum (DMSO d_6) : 0.28 (m, 2H) ; 0.72 (m, 2H) ; 2.29 (s, 6H) ; 3.5 (s, 2H) ; 4.8 (s br, 1H) ; 6.96 (s, 1H) ; 7.34 (s, 2H) ; 9.3 (s br, 1H) ; 11.74 (s br, 1H).
Gc	69%	438	^{1}H NMR spectrum (DMSO d_6) : 0.27 (m, 2H) ; 0.70 (m, 2H) ; 1.27 (s, 6H) ; 1.42 (m, 4H) ; 1.64 (m, 4H) ; 2.3 (s, 6H) ; 3.43 (d, 2H) ; 4.14 (s, 2H) ; 4.59 (s, 2H) ; 4.64 (t, 1H) ; 6.99 (m, 1H) ; 7.41 (s, 2H) ; 11.74 (s br, 1H).

Compound	Yield	MS-ESI $[M+H]^+$	RMN
Gd	60%	538	^{1}H NMR spectrum (DMSO d_6) : 0.17 (m, 2H) ; 0.46 (m, 2H) ; 1.14 (s, 9H) ; 1.29 (s, 6H) ; 1.45 (m, 4H) ; 1.65 (m, 4H) ; 2.3 (s, 6H) ; 3.31 (d, 2H) ; 4.23 (s, 2H) ; 4.59 (m, 3H) ; 7.01 (s, 2H) ; 7.04 (s, 1H).
Ge	65%	437	^{1}H NMR spectrum (DMSO d_6) : 0.35 (m, 2H) ; 0.67 (m, 2H) ; 1.27 (s, 6H) ; 1.43 (m, 4H) ; 1.64 (m, 4H) ; 2.3 (s, 6H) ; 2.63 (d, 2H) ; 4.15 (s, 2H) ; 4.58 (s, 2H) ; 6.99 (m, 1H) ; 7.31 (s, 2H) ; 11.74 (s br, 1H).
GR	90%	667	^{1}H NMR spectrum (DMSO d_6) : 0.38 (m, 2H) ; 0.8 (m, 2H) ; 1.28 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 2.3 (s, 6H) ; 3.17 (m, 2H) ; 4.14 (s, 2H) ; 4.57 (s, 2H) ; 6.98 (m, 1H) ; 7.27 (s, 2H) ; 7.98 (d, 1H) ; 8.51 (dd, 1H) ; 8.76 (d, 1H) ; 11.74 (s br, 1H).

Example 9

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propoxy]-4-(4-phenylpiperidin-1-ylmethyl)-5-(3,5-dimethylphenyl)-1*H*-pyrazole



Example 9

HR

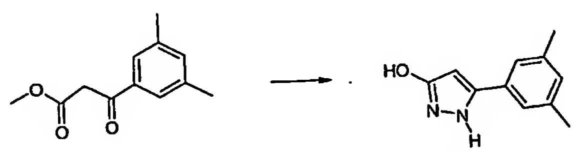
A mixture of 4-phenyl piperidine (98 mg ; 0.6 mmol) and formaldehyde (0.32 ml ; 4.0 mmol ; 37wt% aqueous solution) in water (0.2 ml) and acetic acid (0.2 ml) was stirred for 5 min and treated with **HR** (74 mg ; 0.2 mmol). The mixture was heated at 75°C for 2 h. The solvents were evaporated, MeOH (0.5 ml),water (0.5 ml) and ammonia in MeOH(7N) (0.6 ml) were added and the mixture stirred for a further 3 h. The solvents were evaporated and the residue was purified by preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (80% H_2O) to give **Example 9** as a white solid (75 mg).

Yield : 69%

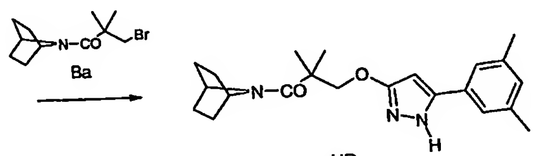
^{1}H NMR spectrum (DMSO d_6) : 1.27 (s, 6H) ; 1.42 (m, 4H) ; 1.6 (m, 6H) ; 1.75 (m, 2H) ; 2.07 (m, 2H) ; 2.32 (s, 6H) ; 2.52 (m, 1H) ; 2.97 (m, 2H) ; 3.16 (s, 2H) ; 4.17 (s, 2H) ; 4.57 (s, 2H) ; 7.02 (s, 1H) ; 7.17 (t, 1H) ; 7.23 (d, 2H) ; 7.28 (t, 2H) 12.1 (s, 1H).

MS-ESI : 541 $[M+H]^+$

The starting material **HR** was prepared as follows:-



Ha



HR

A solution of 4-(3',5'-dimethylphenyl) acetoacetate (12.36 g ; 60 mmol) in EtOH (300 ml) was treated with hydrazine hydrate (5.82 ml ; 120 mmol) and heated under reflux for 3 h. The EtOH was evaporated and the residue triturated with Et_2O. The precipitate was collected, washed and dried to give **Ha** as a white powder (9.54 g).

Yield : 85%

^{1}H NMR spectrum (DMSO d_6) : 2.28 (s, 6H) ; 5.83 (s, 1H) ; 6.93 (s, 1H) ; 7.27 (s, 2H) ; 9.5 (s br, 1H).

MS-ESI : 189 $[M+H]^+$

A mixture of **Ha** (3.1 g ; 16.5 mmol) and **Ba** (5.15 g ; 19.8 mmol) in DMA (40 ml) under argon was treated with K_2CO_3 (4.56 g ; 33.0 mmol). The mixture was stirred and heated at 70°C for 5h. The mixture was poured into sat. aq. $NaHCO_3$, extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$. The solid residue was recrystallised from toluene to give **HR** as a pale yellow solid (2.96 g).

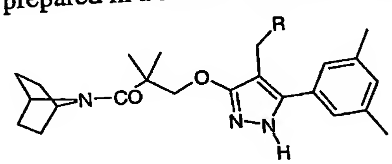
Yield : 49%

^{1}H NMR spectrum (DMSO d_6) : 1.24 (s, 6H) ; 1.41 (m, 4H) ; 1.63 (m, 4H) ; 2.29 (s, 6H) ; 4.09 (s, 2H) ; 4.57 (s, 2H) ; 6.08 (s, 1H) 6.97 (s, 1H) ; 7.31 (s, 2H).

MS-ESI : 368 $[M+H]^+$

Examples 9.1-9.12

The following examples were prepared in a similar manner to Example 9,



H2-13

the table shows the **R** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of Example 9 given above:-

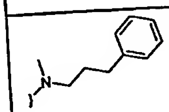
Example 9.1

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	74 ; 0.20	0.25 ; 3.0	131 ; 0.6	White solid	65 ; 54%	598 $[M+H]^+$

Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O).

^{1}H NMR spectrum (DMSO d_6) : 1.25 (s, 6H) ; 1.41 (m, 6H) ; 1.53 (m, 2H) ; 1.58 (m, 4H) ; 2.29 (s, 6H) ; 2.3-2.65 (m, 12H) ; 3.01 (s, 2H) ; 4.15 (s, 2H) ; 4.56 (s, 2H) ; 7.00 (s, 1H) ; 7.17 (m, 3H) ; 7.25 (m, 2H) ; 7.44 (s, 2H) ; 11.9 (s br, 1H).

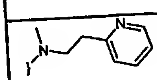
Example 9.2

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	148 ; 0.40	0.32 ; 4.0	270 ; 2.0	White solid	81 ; 39%	529 $[M+H]^+$

Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O).

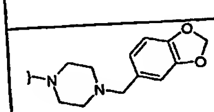
^1H NMR spectrum (DMSO d_6) : 1.23(s, 6H) ; 1.41 (m, 4H) ; 1.60 (m, 4H) ; 1.73 (m, 2H) ; 2.1 (s, 3H) ; 2.27 (s, 6H) ; 2.35 (m, 2H) 2.5-2.7 (m, 2H) ; 3.14 (s, 2H) ; 4.14 (s, 2H) ; 4.56 (s, 2H) ; 6.99 (s, 1H) ; 7.12 (m, 3H) ; 7.23 (m, 2H) ; 7.44 (s, 2H) ; 11.9 (s br, 1H).

Example 9.3

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	80 ; 0.20	0.25 ; 3.0	82 ; 0.6	White solid	27 ; 26%	516 $[M+H]^+$

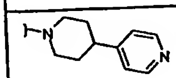
Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (100 to 0% H_2O).

Example 9.4

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	80 ; 0.20	0.25 ; 3.0	132 ; 0.6	White solid	26 ; 22%	600 $[M+H]^+$

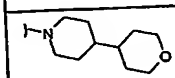
Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (100 to 0% H_2O).

Example 9.5

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	80 ; 0.20	0.25 ; 3.0	97 ; 0.6	White solid	37 ; 34%	542 [M+H]+

Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (100 to 0% H_2O).

Example 9.6

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	80 ; 0.20	0.25 ; 3.0	102 ; 0.6	White solid	21 ; 19%	549 [M+H]+

Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (100 to 0% H_2O).

Example 9.7

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	148 ; 0.40	0.16 ; 2.0	298 ; 2.0	White solid	nd* ; nd*	543 [M+H]+

Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O).

^{1}H NMR spectrum (DMSO d_6) : 1.24 (s, 6H) ; 1.42 (m, 6H) ; 1.54 (m, 2H) ; 1.61 (m, 4H) ; 2.06 (s, 3H) ; 2.25 (s, 6H) ; 2.31 (m, 2H) ; 2.5-2.65 (m, 2H) ; 3. 12 (s, 2H) ; 4.16 (s, 2H) ; 4.56 (s, 2H) ; 6.98 (s, 1H) ; 7.13 (m, 3H) ; 7.22 (m, 2H) ; 7.42 (s, 2H) ; 11.9 (s br, 1H).

<u>Example 9.8</u>

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	148 ; 0.40	0.16 ; 2.0	298 ; 2.0	gum	nd* ; nd*	529 [M+H]+

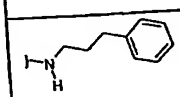
Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O).
^{1}H NMR spectrum (DMSO d_6) : 1.24 (s, 6H) ; 1.42 (m, 6H) ; 1.57 (m, 6H) ; 2.28 (s, 6H) ; 2.5-2.6 (m, 4H) ; 3. 45 (s, 2H) ; 4.16 (s, 2H) ; 4.55 (s, 2H) ; 6.99 (s, 1H) ; 7.14 (m, 3H) ; 7.25 (m, 2H) ; 7.30 (s, 2H) ; 11.9 (s br, 1H).

<u>Example 9.9</u>

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	74 ; 0.20	0.08 ; 1.0	253 ; 1.0	gum	26 ; 24%	543 [M+H]+

Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (80% H_2O).
^{1}H NMR spectrum (DMSO d_6) : 1.24 (s, 6H) ; 1.29 (m, 2H) ; 1.42 (m, 6H) ; 1.53 (m, 2H) ; 1.57 (m, 4H) ; 2.29 (s, 6H) ; 2.5-2.6 (m, 4H) ; 3. 46 (s, 2H) ; 4.16 (s, 2H) ; 4.56 (s, 2H) ; 7.01 (s, 1H) ; 7.15 (m, 3H) ; 7.25 (m, 2H) ; 7.30 (s, 2H) ; 11.9 (s br, 1H).

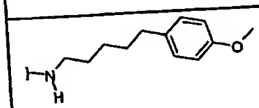
Example 9.10

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	74 ; 0.20	0.08 ; 1.0	162 ; 1.2	White solid	42 ; 20%	529 [M+H]+

Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (80% H_2O).

^{1}H NMR spectrum (DMSO d_6) : 1.24 (s, 6H) ; 1.41 (m, 4H) ; 1.59 (m, 4H) ; 1.69 (m, 2H) ; 2.29 (s, 6H) ; 2.3-2.65 (m, 4H) ; 3.45 (s, 2H) ; 4.16 (s, 2H) ; 4.56 (s, 2H) ; 7.01 (s, 1H) ; 7.157 (m, 3H) ; 7.23 (m, 2H) ; 7.31 (s, 2H) ; 11.9 (s br, 1H).

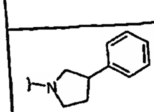
Example 9.11

R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	74 ; 0.20	0.08 ; 1.0	232 ; 1.2	gum	47 ; 41%	573 [M+H]+

Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O).

^{1}H NMR spectrum (DMSO d_6) : 1.24 (s, 6H) ; 1.28 (m, 2H) ; 1.41 (m, 6H) ; 1.49 (m, 2H) ; 1.60 (m, 4H) ; 2.30 (s, 6H) ; 2.3-2.65 (m, xH) ; 3.44 (s, 2H) ; 3.70 (s, 3H) ; 4.16 (s, 2H) ; 4.56 (s, 2H) ; 6.81 (d, 2H) ; 7.01 (s, 1H) ; 7.04 (d, 2H) ; 7.30 (m, 2H) ; 11.9 (s br, 1H).

Example 9.12

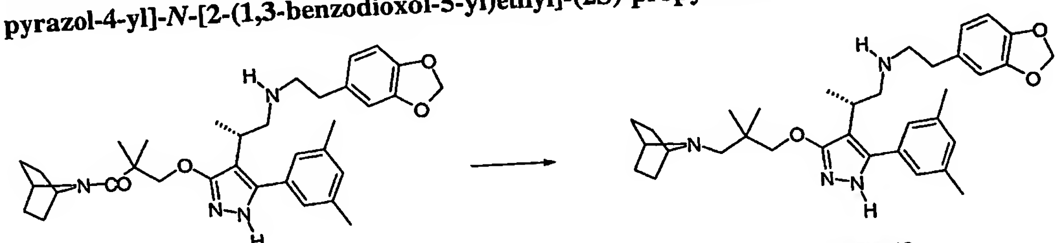
R	HR mg ; mmol	Formaldehyde ; ml ; mmol	Amine mg ; mmol	Prod. Form	Mass mg ; Yield	MS-ESI
	74 ; 0.20	0.08 ; 3.0	97 ; 0.6	White solid	74 ; 69%	541 [M+H]+

Chromato. – Preparative LC/MS chromatography with H_2O/MeCN buffered with ammonium carbonate at pH 8.9 (60% H_2O).

^{1}H NMR spectrum ($CDCl_3$) : 1.34 (m, 6H) ; 1.45 (m, 5H) ; 1.75 (m, 4H) ; 1.9 (m, 1H) ; 2.31 (m, 1H) ; 2.35 (s, 6H) ; 2.5 (m, 1H) ; 2.59 (m, 2H) ; 2.68 (m, 3H) ; 3.39 (dd, 2H) ; 4.28 (s, 2H) ; 4.65 (s, 2H) ; 7.02 (s, 1H) ; 7.16 (m, 3H) ; 7.25 (m, 2H) ; 7.34 (s, 2H) ; 8.9 (s br, 1H).

Example 10

2-[3-(2,2-dimethyl-3-{azabicyclo[2.2.1]heptan-7-yl}propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine



C17 Example 10

A solution of **Example 4** (123 mg ; 0.21 mmol) in THF (3 ml) under argon was treated with a solution of $LiAlH_4$ (420 µl ; 0.42 mmol ; 1M solution in THF). The mixture was heated at 60°C for 1h. The mixture was treated with an excess of Glaubers' Salt ($Na_2SO_4.10H_2O$), filtered and evaporated. The residue was purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (5 to15% MeOH) to give **Example 10** as a white solid (80 mg).

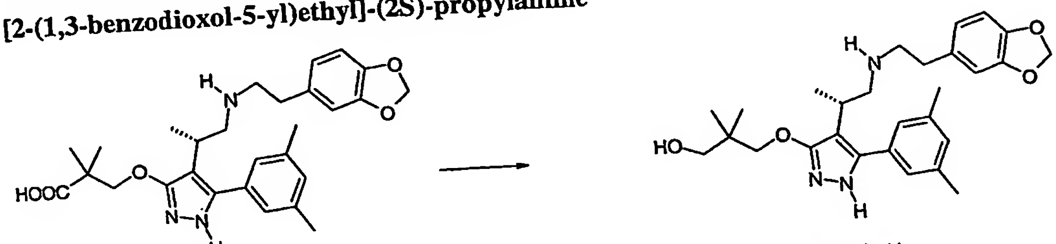
Yield : 68%

^{1}H NMR spectrum (DMSO d_6) : 0.93 (s, 6H) ; 1.18 (d, 3H) ; 1.2 (m, 4H) ; 1.59 (m, 4H) ; 2.19 (s, 2H) ; 2.3 (s, 6H) ; 2.55-2.95 (m, 7H) ; 3.07 (s, 2H) ; 3.86 (s, 2H) ; 5.94 (s, 2H) ; 6.53 (d, 1H) ; 6.66 (s, 1H) ; 6.74 (d, 1H) ; 7.04 (s, 1H) ; 7.05 (s, 2H) ; 11.7 (s br 1H).

MS-ESI : 559 $[M+H]^+$

Example 11

2-[3-(2,2-dimethyl-3-hydroxypropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine



Example 11

JR

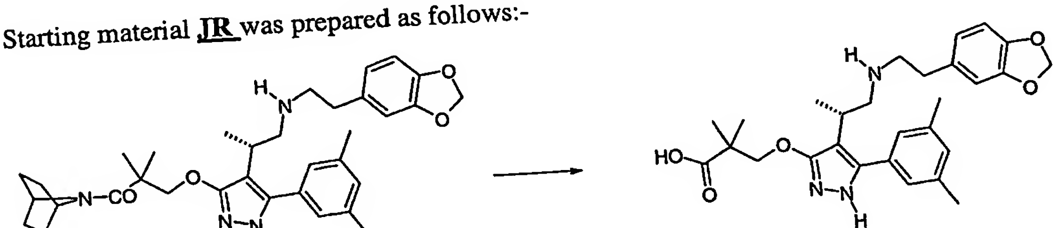
A solution of JR (109 mg ; 0.17 mmol) in THF (2 ml) under argon was treated with a solution of $LiAlH_4$ (350 μl ; 0.35 mmol ; 1M solution in THF). The mixture was heated at 60°C for 1h. The mixture was treated with an excess of Glaubers Salt ($Na_2SO_4.10H_2O$), filtered and evaporated. The residue was purified by flash chromatography eluting with increasingly polar mixtures of $MeOH/CH_2Cl_2$ (0 to15% MeOH) to give **Example 11** as a white solid (68 mg).

Yield : 84%

^{1}H NMR spectrum (DMSO d_6) : 0.92 (s, 6H) ; 1.17 (d, 3H) ; 2.3 (s, 6H) ; 2.5-2.9 (m, 7H) ; 3.27 (s, 2H) ; 3.86 (s, 2H) ; 4.61 (t br, 1H) ; 5.94 (s, 2H) ; 6.53 (d, 1H) ; 6.67 (s, 1H) ; 6.74 (d, 1H) ; 7.03 (s, 1H) ; 7.04 (s, 2H) ; 11.7 (s br 1H).

MS-ESI : 480 $[M+H]^+$

Starting material JR was prepared as follows:-



JR

C17

A solution of Example 4 (205 mg ; 0.35 mmol) in acetonitrile (2 ml) was treated with c.HCl (1 ml) and the mixture was stirred at room temperature for 2h. The mixture was concentrated, extrated with CH_2Cl_2 and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue JR was obtained as a yellow solid (218 mg). It was used directly in the final step of the synthesis of **Example 11** .

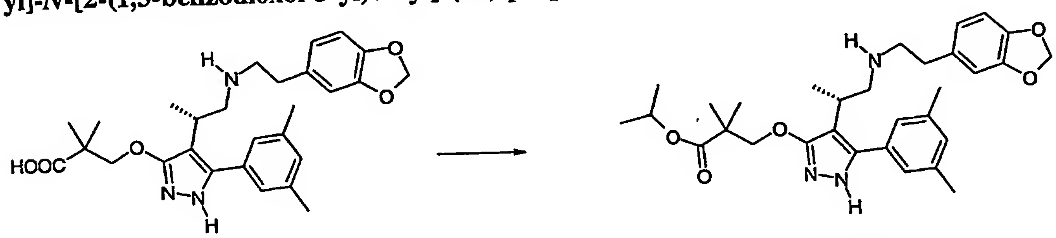
Yield : 80%

^{1}H NMR spectrum (DMSO d_6) : 1.24 (m, 9H) ; 2.33 (s, 6H) ; 2.78 (m, 2H) ; 2.95 (m, 2H) ; 3.14 (m, 3H) ; 4.13 (m, 2H) ; 5.98 (s, 2H) ; 6.62 (d, 1H) ; 6.76 (s, 1H) ; 6.84 (d, 1H) ; 7.05 (s, 2H) ; 7.07 (s, 2H) ; 8.6 (s br, 1H) ; 11.7 (s br 1H).

MS-ESI : 494 $[M+H]^+$

Example 12

2-[3-(2,2-dimethyl-3-oxo3-isopropoxy-propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]-(2S)-propylamine



JR Example 12

A solution of JR (109 mg ; 0.17 mmol) in CH_2Cl_2 (1 ml) was added to a solution of EDCI (37 mg ; 0.19 mmol) and DMAP (5 mg ; cat.) in iPrOH (5 ml). H_2SO_4 (5 drops ; cat.) was added and the mixture was heated under reflux overnight over molecular sieves. The mixture was concentrated and extracted with CH_2Cl_2/water and the organic phase was washed with water, brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with increasingly polar mixtures of MeOH/CH_2Cl_2 (0 to10% MeOH) to give **Example 12** as a yellow gum (59 mg).

Yield : 65%

^{1}H NMR spectrum (DMSO d_6) : 1.16 (m, 6H) ; 1.24 (m, 9H) ; 2.32 (s, 6H) ; 2.8 (m, 2H) ; 2.95 (m, 2H) ; 3.15 (m, 3H) ; 4.16 (dd, 2H) ; 4.88 (m, 1H) ; 5.98 (s, 2H) ; 6.62 (d, 1H) ; 6.74 (s, 1H) ; 6.83 (d, 1H) ; 7.04 (s, 2H) ; 7.07 (s, 2H) ; 11.7 (s br 1H).

MS-ESI : 536 $[M+H]^+$

THERAPEUTIC USES

Compounds of Formula (I) are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in a patient, eg, in men and/or women. To this end, a compound of Formula (I) can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily

suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of 0.1mgkg^{-1} to 30mgkg^{-1} (preferably, 5mgkg^{-1} to 20mgkg^{-1}) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

Buffers, pharmaceutically acceptable co-solvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostatauxe, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The compounds of the invention may be used in combination with other drugs and therapies used to treat / prevent sex-hormone related conditions.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

In the field of medical oncology examples of such combinations include combinations with the following categories of therapeutic agent:

i) anti-angiogenic agents (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in international patent applications publication nos. WO-97/22596, WO-97/30035, WO-97/32856 and WO-98/13354, the entire disclosure of which documents is incorporated herein by reference);

ii) cytostatic agents such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), anti-progestogens, anti-androgens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);

iii) biological response modifiers (for example interferon);

iv) antibodies (for example edrecolomab); and

v) anti-proliferative/anti-neoplastic drugs and combinations thereof, as used in medical oncology, such as anti-metabolites (for example anti-folates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); anti-tumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan,

chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); anti-mitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

The compounds of the invention may also be used in combination with surgery or radiotherapy.

ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following in vitro assays.

Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4°C for 90 minutes to 2 hours.
2. Rapidly filter and repeatedly wash through a glass fibre filter.
3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

From this data, the IC_{50} of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%. Compounds according to the present invention have activity at a concentration from 1nM to 5 μM.

Binding Assay Using Human GnRH Receptor

Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC_{50} which is the compound concentration required to inhibit the specific binding of $[^{125}I]$buserelin to GnRH receptors by 50%. $[^{125}I]$Buserelin (a peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS). The glands are further processed by:-

1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Re-suspension of the cells in culture medium of DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;
9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of 3×10^5 cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5% CO_2/95% air atmosphere at 37°C for 3 to 4 days

Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37% $NaHCO_3$, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 5 μM.